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CEREBRAL CIRCULATION

XIX. THE VAGAL PATHWAY OF THE VASODILATOR IMPULSES

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For several years it has been our good fortune to discuss with Wilder Penfield and his colleagues our laboratory and clinical observations on cerebral circulation. This cooperation developed into a plan to perform a few combined experiments, using the cranial window, as applied in our laboratory, on monkeys whose cerebral sympathetic supply had been unilaterally or bilaterally removed by Penfield. These experiments were carried out in March, 1931. In one of these monkeys, Penfield exposed the medulla oblongata and stimulated the different cranial nerves. To our surprise, no dilatation of the pial artery occurred when the trigeminal root was stimulated close to the medulla, but dilatation was observed when the facial root was stimulated, and when the vagus was stimulated. This experiment was done because ever since the work of Forbes and Wolff,[1] which showed that pial arteries dilate if the vagus nerve in the neck is stimulated, we had been curious to know what the pathway of these dilator impulses might be. A series of experiments on cats and monkeys was then planned to verify and extend this preliminary observation, and the results are presented in this paper and in that by Chorobski and Penfield, which is published in this issue, page 1257.

SUMMARY OF THE LITERATURE

The discovery of the depressor nerve was made by von Cyon and Ludwig[2] in 1866. They believed that the action of the depressor nerve was inhibitory on the vasoconstrictor center. The location of this center was shown by Dittmar[3] to be in the bulb. Bayliss[4] had shown that

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1. Forbes, H. S., and Wolff, H. G.: Cerebral Circulation: III. The Vasomotor Control of Cerebral Vessels, Arch. Neurol & Psychiat. **19**:1057 (June) 1928.
2. von Cyon, E., and Ludwig, C.: Ber. Sachs. Ges. **18**:307, 1866.
3. Dittmar, C.: Ber. Sachs. Ges. **25**:449, 1873.
4. Bayliss, W. M.: J. Physiol. **14**:303, 1893.

stimulating the depressor nerve caused a reflex excitation of the vasodilators. In the light of Sherrington's work, Bayliss [5] elaborated his original concept and applied the principle of reciprocal innervation to vasomotor nerves. That there are specific vasodilators to the blood vessels has been repeatedly shown by many investigators.[6] Hunt [7] has classified the vasodilators into three groups: the sympathetic, parasympathetic and posterior root. Anrep and Evans [8] showed that stimulating the chorda tympani caused vasodilatation in the tongue.

Forbes and Wolff [1] showed that stimulating the sympathetic trunk in the neck brought about a constriction of the pial arteries, and that stimulation of the vagus (depressor) caused a reflex dilatation of the pial arteries. Stöhr,[9] Hassin [10] and Clark and others [11] did histologic studies on the nerves in the cerebral blood vessels. Penfield [12] has recently demonstrated the presence of nerve fibers on the blood vessels of the brain, and he concluded that from a morphologic point of view intracerebral vasomotor reflexes were possible. So far as we know, there have been no physiologic studies on the vagal dilator paths to the pial vessels.

METHOD

The experiments are simple in theory. Forbes and Wolff [1] have observed repeatedly that faradic stimulation of the vagus nerve in the neck resulted in dilatation of the pial artery. We planned to follow the vagus (depressor) nerve up to the medulla causing *afferent* dilator impulses by stimulating at different points. Then by stimulation of the cranial nerves leaving the medulla, we planned to find along which of these the *efferent* impulses traveled to the cerebral vessels. The difficulty lies in the exposure of these cranial nerve roots in the cat (the 5 monkeys were much easier); the medulla was so exposed that an electrode could be used accurately and selectively on one root while an assistant watched a pial artery under the microscope. Obviously, the long anesthetization

5. Bayliss, W. M.: Proc. Roy. Soc., London, s. B. **80**:339, 1908.

6. Golz, F., and Freusberg, A.: Arch. f. d. ges. Physiol. **9**:174, 1874. Ranson, S. W., and Billingsley, P. R.: Am. J. Physiol. **40**:571, 1916. Feldberg, W., and Schilf, E.: Arch. f. d. ges. Physiol. **212**:365, 1926.

7. Hunt, R.: Am. J. Physiol. **45**:197, 1918.

8. Anrep, G. V., and Evans, C. L.: J. Physiol. **54**:10, 1920.

9. Stöhr, Philipp, Jr.: Mikroskopsische Anatomie des vegetativen Nervensystems, Berlin, Julius Springer, 1928.

10. Hassin, G. B.: The Nerve Supply of the Cerebral Blood Vessels in the Vegetative Nervous System, Baltimore, Williams & Wilkins Company, 1930.

11. Clark, S.: J. Comp. Neurol. **48**:247, 1929. Gulland, L.: Brit. M. J. **2**:781, 1898. Huber, G. C.: J. Comp. Neurol. **9**:1, 1899. Hunter, W.: J. Physiol. **26**: 465, 1900.

12. Penfield, W.: Intracerebral Vascular Nerves, Arch. Neurol. & Psychiat. **27**:30 (Jan.) 1932.

and many operative procedures (tracheotomy, cerebral trephining and insertion of the window, cistern puncture and suboccipital craniotomy with exposure of the medulla) often ended in the death of the animal before observations could be made, or sometimes the animals had so much shock that stimulation of autonomic nerves had no regular and significant effect. The data presented are taken only from animals in good condition that showed repeatedly that their vasomotor nerves would react to weak electrical stimuli. All other observations were discarded.

The method of placing a window in the skull, and of observing microscopically pial vessels thus made visible, has been described in detail by Forbes.[13]

The exposure of the nerve to be stimulated was carried out in various ways. The vagus and sympathetic nerves in the neck were exposed in the tracheotomy wound. The roots of the ninth, tenth, eleventh and twelfth cranial nerves were exposed fairly easily by an ordinary suboccipital craniotomy. The roots of the ninth and twelfth nerves, however, were often difficult to find and isolate. To expose the roots of the fifth and eighth nerves, the craniotomy had to be extended forward on one side, and the large venous sinuses encountered had to be carefully circumvented or plugged with wax. For the special exploration of the seventh nerve, various approaches were made: exposing the root at the medulla first, and following it out into the middle ear; or reversing the process, i. e., starting by exposing the middle ear; the facial nerve and geniculate ganglion were located and the medulla later exposed if necessary. The roots of the sixth and fourth nerves were never satisfactorily exposed and stimulated. The root of the third nerve was reached only three times, in 2 cats and 1 monkey. Several unsuccessful attempts were made to stimulate it through an incision in the roof of the mouth; the successful approach was by a wide lateral exposure, the electrode being applied to the nerve after the pons and midbrain had been slightly lifted and rotated.

Faradic stimulation was applied with a unipolar electrode, the other electrode being placed in a leg muscle. The induction coil was that described by Forbes and Wolff.[1]

Blood pressure was recorded in some experiments, but not in all. It was not considered necessary always to observe the pressure because so many experiments have been done by Forbes and his co-workers, with largely uniform results, that it seemed established that stimulation of the vagus nerve in the neck typically causes a fall in blood pressure and a rise in cerebrospinal fluid pressure concomitant with the dilatation of the pial vessels.

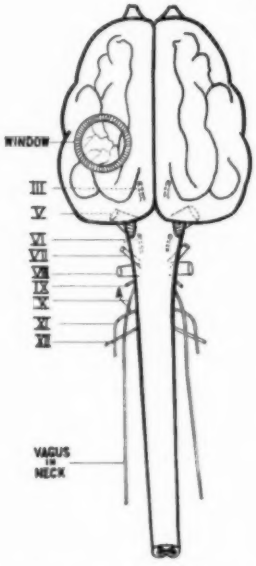
In the earlier experiments the animals were anesthetized by the intraperitoneal injection of 8 cc. of 1 per cent amytal (Lilly) in sodium hydroxide per kilogram of body weight. In several experiments, dial-Ciba, 0.55 cc. per kilogram, was given intraperitoneally. In some of the later experiments ether and morphine were used. The animals were kept under ether during the operative procedure and then given from ¼ to ½ grain (0.016 to 0.032 Gm.) of morphine sulphate subcutaneously. The ether was then removed and the morphine was sufficient to keep the animals in anesthesia. It is known that the anesthesia used has a definite effect on the reaction of the nerve to stimulation and on the size of the pial vessel. In these experiments, our greatest quantitative changes were obtained in the later experiments during morphine anesthesia.

13. Forbes, H. S.: The Cerebral Circulation: I. Observations and Measurement of Pial Vessels, Arch. Neurol. & Psychiat. **19**:751 (May) 1928.

OBSERVATIONS

The observations are summarized in the accompanying table and in figures 1, 2, 3, 4 and 5. Some comments on each procedure are included under the headings of the different nerves stimulated.

Third Cranial Nerve.—As mentioned under "Method," this was a difficult nerve to expose and stimulate. It was satisfactorily accomplished in only 3 animals (2 cats and 1 monkey), and 10 stimulations were made; 9 of them gave no change, but after 1 there was a slight constriction of the observed artery (3 per cent of its diameter).



CRANIAL NERVE	NUMBER OF TRIALS	RESULTS OF STIMULATION (25 CATS, 4 MONKEYS)	
III	10	NO CHANGE	9
		SLT CONSTRICTED	1
V	38	NO CHANGE	38
VII	147	DILATED	122
		NO CHANGE	25
VIII	25	NO CHANGE	25
IX	14	NO CHANGE	14
X	41	DILATED	33
		NO CHANGE	8
X WITH III CUT	16	NO CHANGE	16
X PERIPHERAL TO CUT AT A	20	NO CHANGE	20
X CENTRAL TO CUT AT A	22	DILATED	19
		NO CHANGE	3
XI	42	NO CHANGE	42
XII	17	NO CHANGE	17

Fig. 1.—Diagram of a cat's forebrain and medulla (the cerebellum is not shown to simplify the sketch). Tabulation of results from stimulating the cranial nerves close to the midbrain and hindbrain.

Fourth Cranial Nerve.—By our method of operation, we were unable to expose the trochlear nerve in the cat and stimulate it. In the 3 monkeys, no attempt was made.

Fifth Cranial Nerve.—It was our original expectation that the pathway of the dilator impulses to the cerebral vessels would be found leaving the medulla oblongata with the trigeminal nerve. This was definitely found not to be the case in 11 cats and 2 monkeys. Many more stimulations of the fifth nerve were made than are recorded in the protocols, all with negative results. The protocols show 38 trials in 13 animals, with no change in the caliber of the pial artery after any stimulation. This was one of the easiest nerves to stimulate, and we feel as sure of the results as one can with these methods.

Sixth Cranial Nerve.—No satisfactory exposure of this nerve was made.

Eighth Cranial Nerve.—In 6 cats and 2 monkeys 25 stimulations of the eighth nerve failed to cause any change in the pial vessels. Cutting the eighth nerve did not interfere with the dilatation of the pial vessels from stimulation of the vagus nerve in the neck.

Ninth Cranial Nerve.—This was a rather difficult nerve to isolate, but 14 stimulations in 5 cats and 1 monkey gave no change in the pial vessels in any trial.

Eleventh Cranial Nerve.—This is one of the most easily stimulated of the cranial nerves; it was tried again and again with obvious contraction of the muscle of the neck, but no change in the pial vessels. The records show 42 trials in 11 cats and 1 monkey with no change in the diameter of the blood vessels.

Twelfth Cranial Nerve.—Stimulation of this nerve in 5 cats, 17 trials in all, showed no change in the pial vessels.

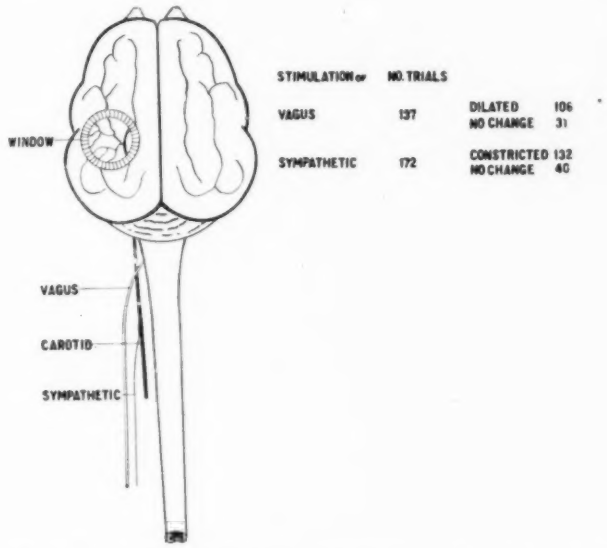


Fig. 2.—Diagram of the ipsolateral sympathetic and vagus experiments of Forbes and Wolff with added data by us. The stimulus was applied to the same side of the animal as the window.

Tenth Cranial Nerve.—In previous experiments by Forbes and his collaborators, the vagus nerve was stimulated in the neck 91 times in 29 animals, with dilatation of the pial artery, 73 times, and no change 18 times. In no case was vasoconstriction observed. Our own observations cover many more observations than are recorded, for this was our regular preliminary procedure, but in the records are results of 41 trials on 19 animals, 33 of which caused dilatation and 8 no change. Our observations, added to those of Forbes, totaled 137 trials in 48 animals, with 106 dilatations and 31 in which there was no change. Of our 41 trials, 36 were with the electrode on the vagus in the neck (point *1*, figure 4); in 6 the electrode was on the ganglion nodosum; all 6 of these caused dilatation. The amount of dilatation of the artery varied from 8 per cent of the diameter to 25 per cent, the average change being 14 per cent. With the vagus nerve cut near the medulla (at

A, figure 1), proximal to the ganglion nodosum, stimulation of the central stump (at point *2*, figure 4) gave dilatation of the pial artery as usual. In 4 animals there were 22 trials, with dilatation 19 times and no change 3 times. When the nerve was stimulated peripheral to the cut (*A*), there was no change in the diameter of the vessel (20 trials in 5 cats).

When the facial nerve was cut close to the medulla (point 3, figure 4) stimulation of the vagus caused no dilatation of the vessels of the pia. This was tried 20 times in 5 cats, with no change in the diameter of the vessels seen under the microscope.

In order to see whether the impulses which traveled up the vagus to the medulla affected only the ipsolateral hemisphere, or both hemispheres, the right vagus nerve was stimulated at the neck in 7 cats and 2 monkeys, the window being over the left cerebral hemisphere; 29 stimulations with this arrangement gave 21 dilatations, and

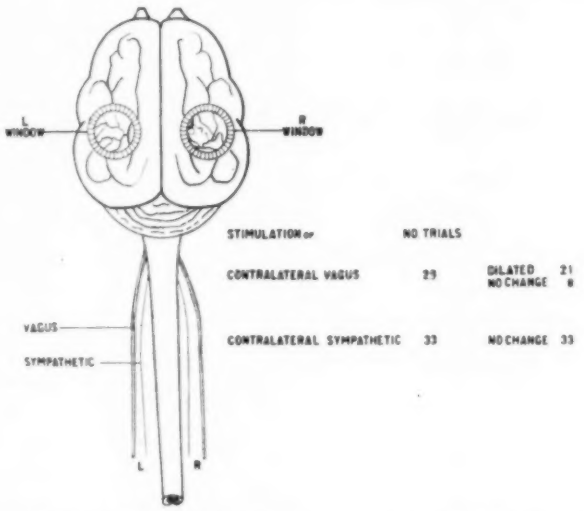


Fig. 3.—Diagram of the contralateral vagus and sympathetic experiments. The stimulus was applied to the side of the neck opposite the window.

no change 8 times. The amount of dilatation was from 4 to 36 per cent of the diameter of the artery observed, the average being 14 per cent as in the ipsolateral hemisphere.

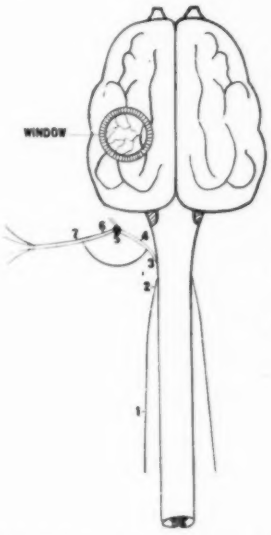
Cervical Sympathetic Nerve.—This nerve has been shown regularly to cause constriction of the pial arteries of the ipsolateral hemisphere (third, ninth and seventh nerves). To compare its action with that of the vagus, the right (contralateral) sympathetic nerve was stimulated in 8 cats and 2 monkeys, after inserting the window in the skull over the left cerebral hemisphere; 33 stimulations failed to give any change in the diameter of the pial vessels.

Seventh Cranial Nerve.—In 21 cats and 4 monkeys, the facial nerve was stimulated between its exit from the medulla and the geniculate ganglion. There were 147 stimulations, and 122 of these caused dilatation of the pial artery, while in 25 there was no change. The average amount of dilatation was 16 per cent, the lowest being 4 and the greatest dilatation being 60 per cent. These great changes were

observed in the last animals operated on, when we had learned to use less amytal for anesthesia and to work more quickly. With the facial nerve cut close to the medulla and with the electrode stimulating the nerve between the cut and the geniculate ganglion (point *4*, figure 4), the dilatation was regularly obtained as in the intact nerve (23 trials on 4 cats and 1 monkey gave 18 dilatations, ranging from 4 to 20 per cent of the artery diameter). Stimulation of the central stump of the vagus (between the medulla and the cut) in these five animals gave no dilatation (10 trials).

The facial nerve was then cut just peripheral to the geniculate ganglion (point *6*, figure 4). Stimulation of the facial nerve peripheral to this point (point *7*, figure 4) caused no change in the artery; this was tried 14 times in 4 cats.

Another check was made by stimulating the vagus in the neck as usual; after the dilatation of the pial artery was regularly obtained, the facial nerve was cut



STIMULATION AT	NO. TRIALS		
1 WITH VII INTACT	41	DILATED	33
		NO CHANGE	8
2 WITH VII INTACT	22	DILATED	19
		NO CHANGE	3
1 WITH VII CUT AT 3	16	NO CHANGE	16
3 WITH VII INTACT	124	DILATED	104
		NO CHANGE	20
3 WITH VII CUT AT 4	10	NO CHANGE	10
4 WITH VII CUT AT 3	18	DILATED	16
		NO CHANGE	2
7 WITH VII CUT AT 6	14	NO CHANGE	14

Fig. 4.—Tabulation of results from stimulating the vagus and facial nerves. The numbers indicate loci of stimulation on various segments of the facial nerves. For complete data see the accompanying table.

near its exit from the medulla and the vagus in the neck again stimulated (stimulus at *1*, cut at *3*, figure 4). This was tried 16 times on 4 cats and 1 monkey, and in no case was any change seen in the artery after cutting the facial nerve, although conspicuous dilatation had been previously recorded in the same animals on stimulating the vagus before the seventh nerve had been cut.

PROTOCOLS

Protocol A.—A male cat weighing 3 Kg. was given 25 cc. of 1 per cent amytal intraperitoneally. A tracheotomy was done, the vagus and sympathetic were exposed on both sides of the neck, and the window was screwed into the left side of the skull after the dura had been cut. A straight manometer was connected to the cisterna magna for readings of the cerebrospinal fluid pressure, and

a mercury manometer was connected with a cannula in the femoral artery for blood pressure readings. When the operative procedures were completed, the diameter of the pial artery was 468 microns, the cerebrospinal fluid pressure was 78 mm. of Ringer's solution, and the blood pressure was about 70 mm. of mercury. The vagi and sympathetics of both sides were tied, cut and prepared for electrical stimulation of an induced faradic current through a bipolar electrode. During the preliminary five minute period preceding stimulation, the arterial diameter remained constant at 468 microns. The cerebrospinal fluid pressure averaged about 74 mm. of Ringer's solution, while the blood pressure averaged from 50 to 60 mm. of mercury. After a satisfactory preliminary period, the right (contralateral) sympathetic was stimulated for sixty seconds with the secondary coil at 9.

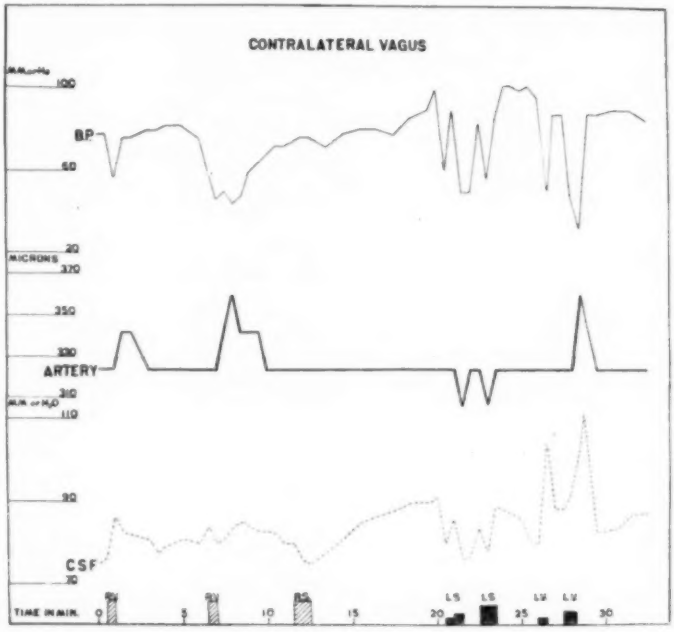


Fig. 5.—The effect of stimulating the right and left vagi and sympathetics on the pial artery, systemic blood pressure (*B.P.*) and cerebrospinal fluid pressure (*C.S.F.*). The window is over the left cortex. Stimulating both the right vagus (*R.V.*) and the left vagus (*L.V.*) resulted in dilatation of the pial artery. Stimulating the contralateral right sympathetic (*R.S.*) had no effect, whereas stimulating the left sympathetic (*L.S.*) resulted in the usual contraction of the pial artery. See protocol A.

During this stimulation the artery dilated, and its diameter increased from 468 to 540 microns, an increase of 12 per cent. The cerebrospinal fluid pressure rose from 78 to 92 mm. of Ringer's solution, and the systemic blood pressure dropped from 64 to 34 mm. of mercury. On removal of the electrode, readings of the arterial diameter cerebrospinal fluid and blood pressures approached their preliminary values. After five minutes, the right (contralateral) sympathetic and vagus were stimulated with the secondary coil at 8. Stimulating the contralateral sympathetic

gave no change in the arterial diameter; there were a slight increase in cerebrospinal fluid pressure and a rise in blood pressure from 60 to 96 mm. of mercury, and respirations became more rapid and deeper. When the right (contralateral) vagus was stimulated, the pial artery dilated from 468 to 504 microns, an increase of 8 per cent; the cerebrospinal fluid pressure rose from 66 to 76 mm. of Ringer's solution, and the blood pressure took a marked drop from 88 to 34 mm. of mercury. On removal of the stimulus, the artery constricted to its preliminary value, the cerebrospinal fluid pressure dropped back to its preliminary value, and the systemic blood pressure slowly climbed back to its original value. When the artery had been constant for two minutes, as a control, the left (ipsolateral) vagus was stimulated with a slight current. No change occurred in the arterial diameter; the cerebrospinal fluid pressure rose from 78 to 102 mm. of Ringer's solution; the blood pressure also dropped from a level of 100 to 56 mm. of mercury. The left (ipsolateral) vagus was stimulated with a more powerful stimulus for thirty seconds. This resulted in an increase in the arterial diameter from 468 to 486 microns. There was a slight rise in cerebrospinal fluid pressure followed by a slight drop and little change in the blood pressure. After the artery had attained its preliminary value and had been constant for five minutes, the left (ipsolateral) sympathetic was stimulated for sixty seconds with the coil at 8. This resulted in a decrease in arterial diameter from 468 to 414 microns, a decrease of 14 per cent; the cerebrospinal fluid pressure dropped from 79 to 69 mm. of Ringer's solution, and the blood pressure rose from 56 to 72 mm. of mercury. This experiment showed that stimulation of both ipsolateral and contralateral vagi gave a reflex dilatation of the pial vessels, whereas vasoconstriction was elicited only on stimulation of the ipsolateral sympathetics.

Protocol B.—A female monkey (Macacus rhesus) weighing 2.5 Kg. was given 20 cc. of 1 per cent amytal intraperitoneally. The vagus and sympathetic on the left were exposed ready for tying and cutting before stimulation. The window was put into the left side of the skull, and an artery in the pia was selected for measurement. At this point a left suboccipital operation was done, removing the bone, cutting the dura and exposing the hindbrain so that the cranial nerves could be seen just as they emerged from the hindbrain.

After the artery had been constant at a diameter of 90 microns for ten minutes, the left vagus was tied, cut and stimulated with a unipolar electrode from a Harvard inductorium. On stimulating the left vagus for thirty seconds, the pial artery dilated from 90 to 99 microns, a change of 10 per cent. After removal of the stimulus, the arterial diameter decreased until it had returned to its preliminary level of 90 microns. A larger artery was then selected, which had a diameter of 216 microns. After a preliminary period of five minutes, the left vagus in the neck was stimulated for thirty seconds. The artery dilated from 216 to 232 microns, a change of 8 per cent. When the stimulus was removed, the artery returned to its preliminary diameter of 216 microns. At this point the animal was put under artificial respiration and another artery was selected, measuring 108 microns. The respirations were shut off by pinching the tube of compressed air going to the animal for thirty seconds. The artery became cyanotic, but there was no change in its diameter. After two minutes, the left vagus was stimulated again for thirty seconds with the secondary coil at 11, and the artery dilated from 108 to 126 microns, a change of 16 per cent. When the stimulus was removed, the artery returned to its preliminary level.

After an hour, the artificial respiration was removed and an artery was selected, which measured 126 microns. The eleventh nerve was stimulated twice just as it left the hindbrain. In both cases there were movements of the shoulder. The

artery did not change. The electrode was then placed on the seventh nerve (point *3*, (figure 4) as it emerged from the hindbrain. With the coil at 11, a stimulation of thirty seconds' duration caused a dilatation of the artery from 126 to 144 microns, a change of 14 per cent. When the stimulus was removed, the artery returned to its preliminary diameter. After three minutes the seventh nerve was again stimulated; this time some current spread to the eleventh nerve, which caused a slight movement of the shoulder. The pial artery dilated from 126 to 135 microns, a change of

Summary of Data *

Locus of Stimulation	Number of Animals	Number of Trials	Effect of Stimulation on Pial Artery	Percentage Change in Diameter of Pial Artery: Low	High	Average
Sympathetic in neck:						
Ipsolateral	58	172	Constriction 132 No change 40	1.3	20	8.03
Contralateral	10	33	No change 33			
Vagus:						
Ipsolateral	48	137	Dilated 106 No change 31	3.0	50	14.5
Contralateral	9	29	Dilated 21	4.0	36	14.0
Central to A	4	22	Dilated 19 No change 3	3.0	22	15.5
Peripheral to cut at A	5	20	No change 20			
With VII nerve cut	5	16	No change 16			
III nerve	3	10	No change 9 Slight constriction 1			
V nerve	13	38	No change 38			
VII nerve:						
Total	25	147	Dilated 122 No change 25	4.0	60	16.6
Point 3 with VII nerve intact	21	124	Dilated 104 No change 20	4.0	60	17.0
Point 3 with cut at 4	5	10	No change 10			
Point 4 with cut at 3	6	18	Dilated 16 No change 2	4.0	20	12.0
Point 7 with cut at 6	4	14	No change 14			
VIII nerve	8	25	No change 25			
IX nerve	6	14	No change 14			
XI nerve	10	42	No change 42			
XII nerve	5	17	No change 17			

* Including the vagus and sympathetic experiments by Forbes and Wolff. The letters and figures refer to figures 1 and 4.

7 per cent. The eleventh nerve was stimulated once more, with consequent movement of the shoulder girdle and no change in the arterial diameter. The medulla was further exposed, and there was some hemorrhage, and the artificial respiration was again resumed. The arterial diameter was 135 microns. The eleventh nerve was again stimulated, with consequent movement of the shoulder and no change in the pial artery. The seventh nerve was stimulated 3 times with the secondary coil at 11. Each stimulus caused movements of the facial musculature and a dilatation of the pial artery of 7 per cent. The seventh and eighth nerves were cut close to the medulla. Immediately on cutting these nerves the artery dilated from 135 to 144 microns for a few seconds, and then returned to its preliminary level.

The seventh nerve was then stimulated peripheral to the cut (point *4* with cut at *3*, figure 4). This resulted in a contraction of the ear muscles and a dilatation of the pial artery from 135 to 149 microns, a dilatation of 10 per cent. After the stimulus was removed, the vessel slowly returned to its preliminary level of 135 microns. After five minutes the eleventh nerve was stimulated. This resulted in *no* change in the diameter of the pial artery. Following this, the vagus in the neck was stimulated twice, and there was no change in the diameter of the pial artery, whereas dilatation was obtained earlier in the experiment before the seventh nerve had been cut.

This experiment shows that dilatation of the pial artery could be obtained reflexly by stimulating the vagus and directly by stimulating the seventh nerve as it left the hindbrain. Dilatation was also obtained when the peripheral end of the cut seventh nerve was stimulated directly. After the seventh nerve had been cut, the reflex dilatation on stimulating the tenth nerve was not obtained. Stimulating the eleventh cranial nerve before and after the seventh nerve was cut gave no change in the diameter of the pial artery.

COMMENT

A synthesis of all these observations indicates that vasodilator impulses may be initiated by faradic stimulation of the vagus nerve in the neck; these impulses then pass up the vagus trunk to the medulla oblongata; here they proceed to both facial nuclei (by an intramedullary route as yet unknown) and travel out along the facial nerves as far as the geniculate ganglia. Just what the pathway is from here to the cerebral arteries has not been investigated by us. Penfield and Chorobski have been studying this phase of the problem, and their results are reported in a paper published simultaneously with this one. In standard textbooks on anatomy, connections between the geniculate ganglion and the meningeal and cerebral arteries are described, but Chorobski's recent work supersedes these by showing a direct anatomic pathway which leaves the facial nerve in the vicinity of the geniculate ganglion and passes to the internal carotid artery. The work of Stöhr [9] and Hassin,[10] showing nonmyelinated nerves accompanying the pial vessels, and Penfield's [12] recent description of nerve fibers on intracerebral blood vessels complete the anatomic demonstration. It seems that the vasodilator impulses follow these autonomic nerves from the geniculate ganglion to large cerebral arteries at the base of the brain and then spread and branch with each vessel, just as do the sympathetic nerves that join the carotid artery at a lower level.

The proposition might be advanced that these impulses were not active, but inhibitory vasodilator impulses, and that the vessels dilate because the tonic vasoconstriction effect of the sympathetic innervation was inhibited by vagus stimulation. At present there is no absolute proof that the autonomic innervation to the pial vessels is actively vasodilator in character. Forbes and Wolff [1] showed that vasodilatation followed

vagus stimulation even after both cervical sympathetic nerves had been cut. To demonstrate this conclusively, animals should be prepared by sympathectomy six weeks before the vagus stimulation experiments, to allow for complete degeneration. One of our animals, only, offers evidence on this point. One monkey was operated on by Dr. Penfield, who removed the left stellate and left superior cervical ganglia. After sufficient time had been allowed for complete degeneration, afferent stimulation of the vagus in the neck gave a definite dilatation of the ipsolateral pial arteries. This would lead us to infer that the effect was the result of active dilator impulses rather than the inhibitive effect of the sympathetic, which in this case had degenerated. This observation is in keeping with the recent work of Freeman and Rosenblueth [14] on changes in vasodilator tone in sympathectomized animals. At present it seems to be proved that there is a neural pathway that carries impulses to the cerebral vessels, and that stimulation of this pathway causes vasodilatation of all arteries and many of the larger veins on the surface of the brain.

An objection to this conclusion is that the cerebral vasodilatation may not be caused by autonomic nervous stimulation, but by the fall in blood pressure which almost always accompanies vagus stimulation. It seems more reasonable to suppose that the cerebral vasodilatation and the fall in blood pressure are both results of vagus stimulation, but independent. Evidence that this is the fact was obtained in one of our experiments in which stimulation of the facial nerve was shown to cause dilatation of the pial artery without any concomitant fall in blood pressure. This occurred both with the facial nerve intact and after cutting it close to the medulla. Another experiment also throws light on this point. In this cat, too, dilatation of the pial artery was found to take place repeatedly on stimulating the seventh cranial nerve. In some instances there were no changes in blood pressure, and in others a slight drop in blood pressure was recorded. The magnitude of the dilatation was independent of the change in the blood pressure. The seventh nerve was cut close to the medulla. Stimulating the peripheral end gave a dilatation of the pial artery but no change in blood pressure. Stimulating the central end gave a drop in blood pressure of 18 per cent with no change in the pial artery. Later in the experiment, the blood pressure was lowered 18 per cent, and this did not result in any change in the pial diameter. Moreover, in 14 per cent of Forbes and Wolff's [1] experiments, vasodilatation occurred after vagus stimulation without an accompanying fall in blood pressure.

Still another possible explanation of the vasodilator effect is that respiratory changes also result from vagus stimulation. If this change

14. Freeman, N. E., and Rosenblueth, A : Am. J. Physiol. **98**:454, 1932.

results in lack of oxygen, with accumulation of carbon dioxide, it would cause dilatation of the cerebral vessels. Wolff and Lennox[15] have carefully studied these chemical effects. A comparison of their records with ours shows that the dilatation due to excess of carbon dioxide is conspicuous, but comes on more slowly and lasts longer than the dilatation due to stimulation of the nerves. In our later and better experiments, the artery was seen to expand rapidly within five or ten seconds of the onset of the nerve stimulus, and equally quickly, after cessation of the stimulus the artery would rapidly contract to its original size. After changes in the carbon dioxide content of the inspired air, there was a latent period of one or more minutes before the vessels reacted. Moreover, the same changes due to stimulating the seventh nerve were found to occur in animals under artificial respiration.

It may be said in criticism that all the cranial nerves were not explored, since the fourth and sixth were not exposed and stimulated. This is true, but the fact that cerebral vasodilatation from vagal stimulation stopped when the seventh nerve was cut indicates that (for the arteries observed, at least) the dilator impulses passed along the facial nerve. The nerve from the carotid sinus may also carry vasodilator impulses. It could likewise be conjectured that impulses entering the medulla might pass upward to cerebral centers and thence directly to the cerebral vessels. This theory is so antagonistic to all we know of embryology and physiology that it hardly seems worth investigating. Moreover, the same argument applies here that was used for the fourth and sixth nerves—when the facial nerve is cut, the phenomenon is abolished.

The question of how important this vasomotor control may be in normal cerebral function cannot be answered by these experiments. In the first place, all the animals were under an anesthetic which undoubtedly reduces the normal vasomotor effects. The amount of dilatation observed seems relatively slight when expressed in terms of percentage of artery diameter. If, however, this is translated into terms of blood flow,[16] it will be found that a 22 per cent increase in the diameter of an artery means that the minute volume of blood becomes two and a half times as great as it was before dilatation took place. This is certainly of functional significance, and it is probable that in normal animals greater and more rapid changes take place than in the anesthetized cats and monkeys.

15. Wolff, H. G., and Lennox, W. G.: Cerebral Circulation: XII. The Effect on Pial Vessels of Variations in the Oxygen and Carbon Dioxide Content of the Blood, Arch. Neurol. & Psychiat. **23**:1097 (June) 1930.

16. Cobb, S.: Am. J. M. Sc. **178**:528, 1929.

CONCLUSIONS

Nerve impulses may pass up either vagus nerve trunk to the medulla oblongata, leave the medulla along both facial nerves and travel as far as the geniculate ganglia, and thence along autonomic nerves to the cerebral vessels. Here they cause vasodilatation. Thus, in the brain, as in other organs of the body, there is sympathetic vasoconstriction opposed by parasympathetic vasodilatation. The stimulation of one vagus nerve causes a bilateral cerebral vasodilatation, whereas the stimulation of a cervical sympathetic nerve causes only an ipsolateral vasoconstriction.

CEREBRAL VASODILATOR NERVES AND THEIR PATHWAY FROM THE MEDULLA OBLONGATA

WITH OBSERVATIONS ON THE PIAL AND INTRACEREBRAL VASCULAR PLEXUS

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AND

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MONTREAL, CANADA

A crucial experiment in the laboratory of neurology of the Boston City Hospital in which we cooperated with Cobb, Forbes and Finesinger indicated that the efferent pathway for vasodilatation of cerebral arteries would be found in the facial nerve. Returning to Montreal, we made a study [1] of the seventh cranial nerve and its connections, and found that there is a direct nerve bundle to the pericarotid plexus which leaves the facial nerve at the geniculate ganglion. Simultaneous physiologic [2] experimentation, carried out independently by Cobb and Finesinger, led them to conclude also that the pathway must leave the facial at the geniculate, as described in their contribution to be found in this issue, page 1243.

Following previous work on the perivascular nerves of the brain (Penfield, 1931), we had found that complete sympathectomy did not markedly reduce the total number of perivascular nerve fibers. Therefore, having an excellent method of staining vascular nerves at hand, we had set ourselves the question, What other sources are there for these nerve fibers? The connection with the seventh nerve already mentioned proves now to be only a partial answer to this question, as will be described, but it seems best to present this together with certain physiologic and histologic studies without further elaboration.

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Read at the Fifty-Eighth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 6, 1932.

1. The rôle played by each author is as follows: The anatomic studies of the vasodilator tract were carried out by Chorobski and the histologic studies of the pial and intracerebral vascular nerves by Penfield. The physiologic experiments were a common undertaking.

2. The authors are committed to the use of the terms "physiological," "pathological" and "anatomical" instead of "physiologic," "pathologic" and "anatomic," but in accordance with the editorial style of the ARCHIVES the words have been modified in each instance to read "physiologic," "pathologic" and "anatomic."

REVIEW OF THE LITERATURE

Nervus Facialis.—In the lower vertebrates the facial nerve innervates the branchial musculature and thus has to do with respiratory movements. The gradual adaptation of these muscles to movements of facial expression in mammals has not altered their innervation. From an anatomic point of view, the central nuclei of the facial nerve proper and of the nervus intermedius of Wrisberg are both situated in the visceral area of the medulla oblongata along with the nucleus of the vagus. Consequently, anatomists generally (Johnston, 1906; Streeter, 1912; Wilder, 1923; Herrick, 1924; Ranson, 1931) have considered the facial nerve to be visceral.

Secretory and vasodilator efferent pathways leave the medulla in the facial nerve to be distributed through two branches, the chorda tympani and the greater superficial petrosal nerve (fig. 1). The chorda tympani innervates the sublingual and submaxillary salivary glands, the fibers being interrupted in their course to the gland tissue by a ganglion on the surface of each of these salivary glands (Bernard, 1858; Langley, 1900). Thus, the nerve fibers each make connection with more than one ganglion cell (Rhinehart, 1918). There is a second secretory innervation for these glands coming from the cervical sympathetic trunk, the secretion produced being of thicker consistency.

A similar dual innervation exists for the blood vessels of the sublingual and submaxillary glands (Bernard, 1858). The chorda tympani supplies vasodilator fibers to these vessels and the cervical sympathetic vasoconstrictor fibers. The mechanism of blood vessel changes and secretion will not be discussed here. The evidence at present seems to favor the view that the vasomotor and the secretory actions are not identical but are subserved by different nerve fibers (Heidenhain, 1872; Barcroft, 1914; Bayliss, 1923; Stavraky, 1931).

The chorda tympani sends vasodilator fibers also to the anterior two thirds of the tongue through the lingual nerve, the vasoconstrictors, on the other hand, reaching the tongue from the cervical sympathetic through the hypoglossal nerve.

A second branch from the facial nerve, the greater superficial petrosal nerve, arises within the petrous portion of the temporal bone at the apex of the geniculate ganglion and passes out through the hiatus of Fallopius, running in a sulcus across the base of the middle cranial fossa to pass beneath the gasserian ganglion and along the side of the internal carotid artery to the vidian canal.

From the pericarotid plexus it receives a sympathetic nerve, the deep petrosal. Together they form the vidian nerve, which ends in the sphenopalatine ganglion. This ganglion contains multipolar nerve cells about which preganglionic fibers terminate in end-nets. It is structurally,

therefore, an autonomic ganglion (Retzius, 1880; von Lenhossék, 1894; Müller and Dahl, 1910; Carpenter, 1912; Rhinehart, 1918; Lassell and Fenton, 1928).

Vasodilator fibers for the nasal mucous membrane leave the facial nerve in the greater superficial petrosal. These are preganglionic fibers, which synapse with nerve cells in the sphenopalatine ganglion (Tschalussow, 1913). Blier (1930) showed that in addition to this innervation there may be some additional vasodilators for the nasal cavity in the sympathetic system, which probably have their ganglionic cell stations in the superior cervical ganglion. But certainly vasoconstriction in the

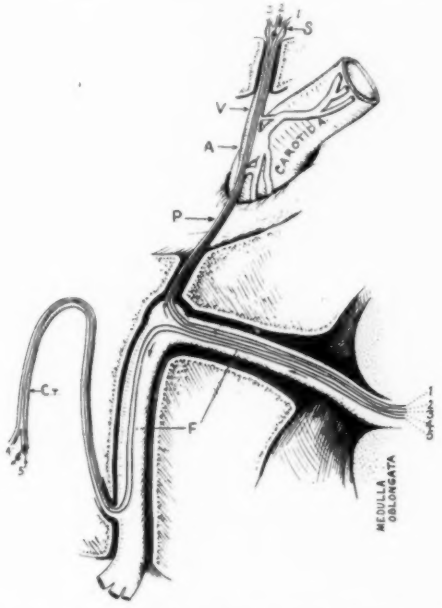

Fig. 1.—Diagram of the efferent nerve fibers of the seventh cranial nerve. *F* indicates the facial nerve; *C.t.*, the chorda tympani; *A*, anastomosis of the greater superficial petrosal nerve with the internal carotid nerve; *V*, the vidian nerve; *S*, the sphenopalatine ganglion; *1* and *1'*, secretory fibers for the lacrimal gland; *2* and *2'*, secretory and vasodilator fibers for the mucous membrane of the nasal cavity; *3* and *3'*, secretory and vasodilator fibers for the mucous membrane of the soft palate; *4* and *4'*, secretory and vasodilator fibers for the tongue; *5* and *5'*, secretory and vasodilator fibers for the submaxillary and sublingual glands.

nasal mucous membrane is produced by the activity of sympathetic nerve fibers which synapse in the superior sympathetic ganglion (Undritz, 1930).

The greater superficial petrosal nerve also carries secretory fibers from the seventh nerve to the ipsolateral lacrimal gland (Landolt, 1903), the pathway passing through the sphenopalatine ganglion to the lacrimal nerve.

In summary, the autonomic efferent fibers so far described in the facial nerve leave the brain stem with the roots of that nerve to be distributed peripherally by two branches, the greater superficial petrosal and the chorda tympani nerves (fig. 1).

In the chorda tympani, secretory fibers join the submaxillary, sublingual and certain accessory salivary glands of the tongue. The vasodilator fibers innervate the blood vessels of these glands and of the tongue. So far as they have been carefully studied, these fibers seem to be preganglionic, being interrupted by peripheral ganglia.

Secretory fibers enter the greater superficial petrosal nerve to supply the lacrimal gland. Vasodilator and secretory fibers pass through this nerve to supply the mucous membrane of the nose, upper pharynx, soft palate, roof of the mouth and upper lip. It has been shown that the sphenopalatine ganglion interrupts the course of the vasodilator fibers, and that the fibers, before reaching this ganglion, may be considered preganglionic, and after the synapse, postganglionic.

Vasodilatation in General.—The nature of vasodilatation in general throughout the body is still a subject of discussion. Gaskell contended (1920) that dilatation of vessels in a muscle was due chiefly to the action of acid metabolites liberated by muscular action, although direct action was possible. Vasodilator fibers to the penis leave the spinal cord in the anterior roots of the second and third sacral nerves (Gaskell, 1887; Sherrington, 1892). It has been conclusively shown that both vasodilators and vasoconstrictors pass to the extremities through the peripheral nerves, and Bayliss (1901, 1902) showed that dilatation could be produced by peripheral stimulation of the posterior spinal roots. This so-called antidromic vascular dilatation takes place in the body dermatome innervated by the nerve in question. By analogy one might well expect that peripheral stimulation of the nervus intermedius of Wrisberg would produce vasodilatation, as this nerve may be considered the posterior root for the seventh nerve with its ganglion, the geniculate, corresponding to the posterior root ganglion of the spinal nerve.

Vasodilatation may, of course, be produced reflexly by afferent stimulation of many different nerves, but in particular of the depressor nerve. Afferent stimulation of this nerve in the neck produces vasodilatation in the mucous membrane of the nose. Stimulation of the vagodepressor trunk produces this effect just the same when the sympathetic trunks have been cut (Martin and Mendelhall, 1915; Fofanow and Tschalussow, 1913). The afferent circuit enters the medulla oblongata, and apparently some portion of the reflex arc may be reached within the brain stem by stimulation of the area postrema on the floor of the fourth ventricle (Ranson and Billingsley, 1916). The efferent

limb of the arc is, of course, within the facial nerve and its branch, the greater superficial petrosal.

A different mechanism seems to be involved in inflammatory vasodilatation. The flushing in this case is prevented only if the peripheral postganglionic fibers are given time to degenerate (Bruce, 1913; Krogh, 1924; Speranskaja-Stepanowa, 1925). This type of vasodilatation is evidently dependent only on an axon reflex, without the interposition of the central nervous system.

A VASODILATOR NERVE BUNDLE TO THE PIAL ARTERIES

In order to present our studies in chronological order, the experiment referred to in the introduction may be described somewhat in detail.

On Nov. 28, 1930, a large male monkey (no. 106) was operated on in Montreal as follows: Under amytal anesthesia, the left superior sympathetic ganglion was exposed, two large anastomosing branches between it and the trunk of the vagus were cut, the ganglion was excised, and the ascending carotid nerves were removed from the internal carotid artery. The left stellate ganglion was exposed. It was excised, together with all branches passing upward on the vertebral artery. The right stellate ganglion lay directly under the corresponding vertebral artery on the other side and sent a large "vertebral nerve" upward on the artery. It was excised with its branches.

This animal, with four others, was taken to the neurologic laboratory of the Boston City Hospital. On March 28, 1931, under dial anesthesia, the following experiment was performed with the help of Drs. Cobb, Finesinger, Forbes and Gage. A Forbes window was placed in the left lateral aspect of the skull. Both vagus nerves were exposed so as to be accessible at a later time, and also the only remaining portion of the cervical sympathetic, the right cervical sympathetic trunk.

The microscope was focused on a pial artery through the window, the micrometer reading of which was 14. The reading of the diameter of the artery, taken every minute for ten minutes, did not change. Right superior sympathetic stimulation caused the right pupil to dilate, but produced no change in the artery beneath the left cortical window.

Stimulation of the proximal branch of the left vagus for one minute caused pulsations in the pial artery to become more marked and the artery redder, and it dilated to a reading of 15, which it maintained for a little over ninety seconds. During stimulation there was spasm of the respiratory muscles. The stimulation was repeated. The animal vomited and coughed, and the artery dilated. Artificial respiration was turned on to the tracheotomy tube to equalize respiration.

The right vagus was then cut, and after control observations on the caliber of the artery, the proximal end was stimulated for sixty seconds. There was conjugate deviation of the eyes to the right and then down. The artery dilated from 14.5 to 15.5 for ninety seconds.

Upward (peripheral) stimulation of the right sympathetic trunk again was without effect except on the ipsolateral pupil and caused increased pulsation in the pial arteries beneath the left window. Stimulation of the left vagus for ninety seconds then produced conjugate deviation to the left and dilatation of the artery from 14 to 15, which continued for eight minutes before returning to 14.

The head was then removed from the clamp, and a suboccipital craniotomy was carried out so as to expose the cranial nerves within the posterior fossa. The head

was replaced and the microscope focused on another artery, the micrometer reading of which was 11. (The constant is 14, which means that the artery was 154 microns in diameter.) Handling the ninth and tenth cranial nerves caused dilatation to 12.5, which returned to 12. Stimulation of the ninth and tenth nerves within the skull for less than one minute (there was some escape to the eleventh as indicated by movement of the shoulder) produced dilatation to 13.5, returning to 12 in two minutes.

Handling of the seventh and eighth nerves caused moderate dilatation. Stimulation of the seventh nerve with small currents gave no change in the vessels. Increase in strength produced enlargement from 12 to 13.5. This was repeated. Stimulation of the fifth nerve caused no change in the vessels.

Stimulation was then carried out on the cranial nerves of the heterolateral side without cutting them. Stimulation of the ninth and tenth pair gave dilatation; stimulation of the fifth, seventh and eighth gave nothing.

The skull window was then removed and placed in the skull at a corresponding point over the right hemisphere. It was now six hours after the window had first been inserted on the left; the blood flow in the arteries was visibly slower. Stimulation of the right sympathetic nerve gave no result, owing possibly to the long exposure of the nerve.

Stimulation of the right facial nerve now caused arterial dilatation from 12.5 to 13. Afferent stimulation of the right vagus caused enlargement from 12 to 12.5. Two further stimulations of the facial nerve were without result, and the circulation of the animal finally came to a stop.

Conclusions.—Afferent stimulation of either ipsolateral or heterolateral vagus in a monkey produces dilatation of the pial arteries. The complete removal of all sympathetic contribution to the vessels of the left cerebral hemisphere four months before must have allowed the postganglionic sympathetic neurons to degenerate. Consequently, this dilator mechanism functions without the aid of the vagosympathetic anastomoses.

Efferent stimulation of the facial nerve produces ispsolateral, but probably not heterolateral, dilatation of the pial arteries.

Anatomy.—Because of the suggestion contained in the foregoing experiment, that an efferent vasodilator pathway runs through the facial nerve, we set ourselves the task of finding the connections of this pathway by anatomic study. Efferent fibers will be described first, as they form the primary subject of this investigation. Certain desultory observations on afferent fibers will be added also.

Efferent Tract: The technic used follows.

A large number of Macacus rhesus monkeys, two Cebus monkeys and a cat embryo were used for the purpose. The animals were anesthetized and the carotids perfused with Ringer's solution followed by 10 per cent neutral or 20 per cent acid commercial formaldehyde. A binocular dissecting microscope was used to follow nerve bundles. After dissection, the nerve plexuses were placed between two blocks of liver or of a spinal cord, and serial sections were cut with the freezing microtome. Appropriate stains were then carried out. The methods most used were hematoxylin and eosin, iron hematoxylin of Loyez, Marchi's osmic acid, Herxheimer's scarlet red and Bielschowsky's or Gross-Bielschowsky's silver methods.

The main anatomic characteristics of the facial nerve in monkeys (fig. 2) are the same as those in man (fig. 1). The nerve leaves the brain stem in company with the nervus intermedius and acusticus and enters the auditory canal, giving off two anastomosing branches to the acoustic nerve. In its course through the fallopian aqueduct, the facial nerve makes a sharp bend, the genu, and at this point lies the geniculate ganglion. This ganglion is chiefly an appendage of the nervus intermedius, although it is closely united at its base to the so-called motor portion of the paired nerves, the facial portion.

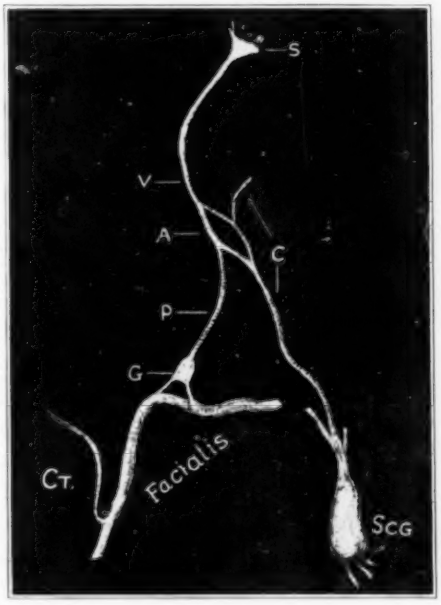

Fig. 2.—Actual dissection of nerves from a Macacus rhesus monkey, the bone and tissue being removed so as to leave the nerves intact with their connections. *SCG* indicates the superior cervical sympathetic ganglion; *C*, the internal carotid removed from the artery; *G*, the geniculate ganglion; *P*, the greater superficial petrosal; *A*, anastomosis; *V*, the vidian nerve; *S*, the sphenopalatine ganglion; *Ct.*, the chorda tympani.

The greater superficial petrosal nerve arises from the apex of the geniculate ganglion and passes anteromesially through the hiatus of the fallopian canal, across the floor of the temporal fossa beneath the gasserian ganglion to the lateral aspect of the internal carotid, just after the emergence of this artery from the petrous portion of the temporal bone. Here it is joined by the lateral ramus of the internal carotid nerve (the deep petrosal nerve) and forms with it the vidian nerve

(fig. 1 *V*), which passes through the canal of that name to enter the sphenopalatine ganglion.

An analysis of the relationship of the greater superficial petrosal to the internal carotid nerve is of primary importance to the purpose of our investigation. There is often a transverse branch joining the two nerves before they unite. The lateral ramus of the internal carotid nerve forms the mesial portion of the anastomosis (fig. 1 *A*). It is made up almost entirely of unmyelinated and small myelinated nerve fibers. The greater superficial petrosal nerve, on the other hand, in addition to fibers of this description, contains also some large and

Fig. 3.—Junction of the internal carotid nerve (*C*) and the greater superficial petrosal nerve (*P*) to form the vidian nerve (*V*) in a Macacus rhesus monkey. The direct tract (*T*) connects the two nerves. Gross-Bielschowsky stain; × 115.

medium myelinated fibers. These large fibers may be traced with ease. Most of them pass on into the vidian nerve. Some, however, enter the carotid nerve and pass both centrad and peripherad in it.

The small myelinated and unmyelinated fibers of the greater superficial petrosal are not traced as easily. Some of them certainly continue into the vidian and others can be seen to enter the internal carotid portion of the anastomosis, especially at its center. From here their further course cannot be traced.

The fibers of the internal carotid, on the other hand, pass in part into the vidian, where they are eventually lost sight of. In part they

leave the anatomosis and continue on the carotid artery. But there is a third portion of these small myelinated and unmyelinated nerves which passes across transversely and enters the proximal portion of the greater superficial petrosal nerve (fig. 3). The bundle may be traced a little way within the nerve. It then is dispersed.

This bundle of small nerve fibers, from its position and direction, must form a direct connection between the pericarotid plexus and the greater superficial petrosal. It might well contain both efferent and afferent fibers.

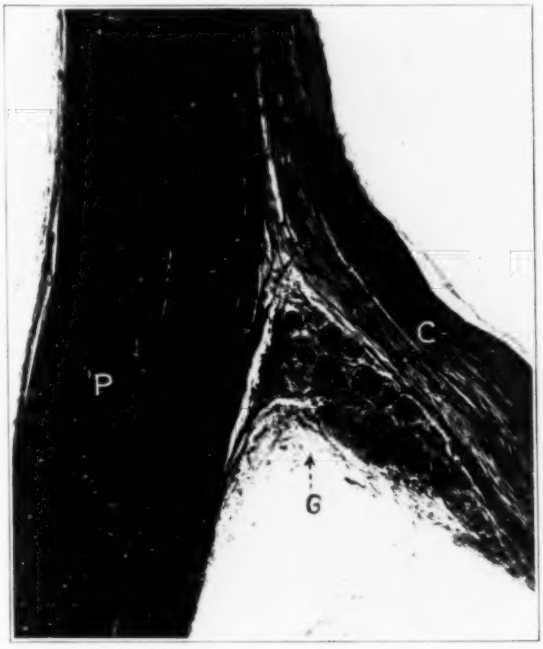

Fig. 4.—Microscopic ganglion on the tract of nerve fibers from the greater superficial petrosal nerve to the internal carotid nerve of a Macacus rhesus monkey. *G* indicates a ganglion; *P*, the greater superficial petrosal nerve; *C*, the internal carotid nerve. Loyez stain; × 110.

On the course of this bundle there is, as a rule, a small ganglion made up of from a few to twenty-eight ganglion cells (fig. 4). There is usually a somewhat smaller aggregation of ganglion cells at the point of exit of the vidian nerve from the anastomosis (fig. 5). There are ganglion cells scattered in twos and threes, or singly, through the anastomosis. These nerve cells resemble those which are often found scattered along on the internal carotid artery in its intracranial course, and still more often in the course of the greater superficial petrosal (fig. 6) and vidian nerves.

Certain connections are accepted: The deep petrosal or internal carotid nerve carries a sympathetic supply into the sphenopalatine ganglion (Winslow, 1749). The greater superficial petrosal nerve is the pathway for sensory impulses, which pass in turn through the sphenopalatine ganglion and the geniculate ganglion. This nerve carries vasodilator and secretory fibers from the facial to the sphenopalatine ganglion.

It remained to be proved whether the pericarotid plexus was connected with the facial nerve by either efferent or afferent fibers.

Fig. 5.—Microscopic ganglion at the exit of the vidian nerve from the anastomosis of the greater superficial petrosal nerve with the internal carotid nerve of a Macacus rhesus monkey. *C* indicates the internal carotid nerve; *V*, the vidian nerve; *G*, a ganglion. Gross-Bielschowsky stain; × 57.

Connection between the carotid and the greater superficial petrosal was suggested very early by Pieschel (1844) in the horse and by Arnold (1851) in the lamb. Arnold, in fact, stated that he could, on occasion, trace a grayish-red bundle from the internal carotid artery backward, closely applied to the greater superficial petrosal and into the genu of the facial nerve. This rather astonishing feat has apparently not been repeated, for although Henle (1868) and Rauber and Kopsch (1909) mentioned anastomosis between the internal carotid and the facial nerve, it is not described by recent anatomists. The belief was (Penzo, 1893;

von Lenhossék, 1894) that this connection carried sympathetic fibers backward into the facial nerve along this tract.

Our Own Studies: Eighteen specimens of the geniculate region of the facial nerve were studied. In two specimens, one from a Macacus rhesus monkey and one from a Cebus monkey, the sections fortunately demonstrated the elements of the origin of the greater superficial petrosal nerve clearly.

In the first specimen one can see that the nervus intermedius, which lies medial to the motor portion of the facial nerve, is actually composed of two bundles, a larger and a smaller. The larger bundle accompanies the motor portion of the seventh nerve closely into the genu, where it turns forward and, spreading out like

Fig. 6.—Ganglion cells in the greater superficial petrosal nerve of a Macacus rhesus monkey. Loyez stain; × 475.

a fan, enters the medial angle of the geniculate ganglion. Apparently, none of the fibers of this bundle passes into the greater superficial petrosal nerve directly.

On reaching the genu, the smaller and more medial of the two bundles turns and, entirely separate from the larger bundle, enters the greater superficial petrosal nerve without interruption (fig. 7). There are no nerve cells on the fibers of this bundle, and it can be stated that the majority, at least, of its fibers have no connection with the cells of the geniculate ganglion. A direct tract (fig. 8) from the facial nerve and the intermedius to the greater superficial petrosal nerve has also been described by other workers (Penzo, 1893; von Lenhossék, 1894; Weigner, 1905; Ramón y Cajal, 1911, and Rhinehart, 1918).

Morphologically, this direct bundle is composed of unmyelinated and myelinated nerve fibers of the same diameter as the fibers in the larger bundle of the intermedius, although the arrangement of fibers is less compact. The diameter of the largest myelinated nerve fibers of the direct bundle is much smaller than that of

Fig. 7.—Direct nerve fiber tract (T_2) from the seventh cranial nerve to the greater superficial petrosal nerve in a Macacus rhesus monkey. *F* indicates the facial nerve; *G*, the geniculate ganglion; T_1, the tract of nerve fibers entering the geniculate ganglion; *P*, the greater superficial petrosal nerve. Hematoxylin and eosin stain; × 42.

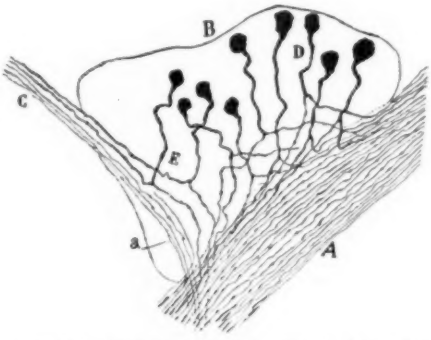

Fig. 8.—Direct tract (*a*) from the facial nerve (*A*) to the greater superficial petrosal nerve (*C*). *B* indicates the geniculate ganglion; *D*, ganglion cells, axis cylinders of which pass into the peripheral portion of the facial nerve; *E*, ganglion cells, axis cylinders of which pass into the greater superficial petrosal nerve. Mouse embryo; Golgi's method, after Cajal (1911).

the largest fibers in the motor portion of the facial nerve or the largest myelinated fibers of the greater superficial petrosal nerve.

In the Cebus monkeys, the fibers of the central portion of the facial nerve and of the nervus intermedius are intermingled so that the two portions cannot be differentiated as in Macacus monkeys. Nevertheless, it could be seen in the Cebus monkey that at the genu a number of small nerve fibers emerge and run mesially and forward to enter directly into the greater superficial petrosal nerve (fig. 9). It so happened that in some of the sections which showed the direct tract best the cells of the geniculate ganglion were absent altogether, because of the fact that they lay in a different plane.

In serial sections which we made of the cat embryo, direct fibers could be seen streaming through between the cells of the geniculate ganglion. These direct fibers could be traced from the root of the facial nerve.

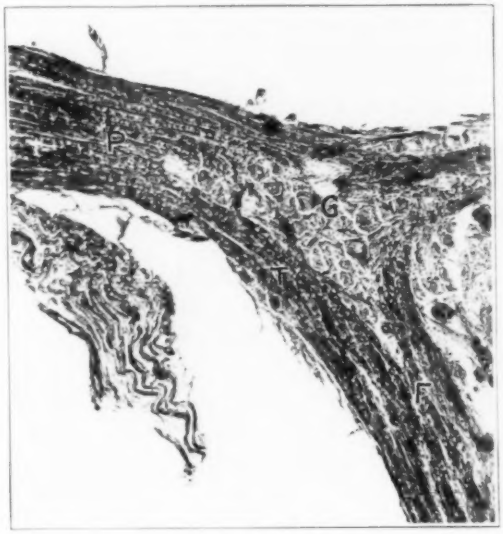

Fig. 9.—Direct nerve fiber tract (*T*) from the seventh cranial nerve (*F*) to the greater superficial petrosal nerve (*P*) of a Cebus monkey. *G* indicates the geniculate ganglion. Gross-Bielschowsky stain; × 77.

Our initial morphologic studies, therefore, showed a direct tract of nerve fibers, made up of unmyelinated and myelinated nerves, which connects the facial and greater superficial petrosal nerves. Further, there is a tract or bundle of similar nerve fibers which connects the greater superficial petrosal nerve with the pericarotid plexus. On this latter tract are to be found ganglion cells.

Experimentally, Vulpian (1878) showed that the section of the central portion of the facial nerve produced degeneration into the greater superficial petrosal nerve. In the reverse direction, Yagita (1914) showed that after section of the vidian nerve not all of the

degeneration stopped at the geniculate ganglion. Some retrograde degeneration was found in nerve cells of the medulla.

To check these observations, the following experiments were carried out:

In fourteen monkeys the facial nerve was cut. After a suitable length of time, the greater superficial petrosal and its connections with the internal carotid and vidian nerves were studied.

The nerve was cut (along with the eighth) within the posterior cranial fossa. Four animals were eliminated as unsatisfactory for one reason or another, which left ten for study. These were killed from ten to thirty days after the operation.

Of these ten animals, satisfactory stains of degenerating myelin were obtained in three. The specimen of ten and of eleven days showed a moderate amount of degeneration, while the specimen of thirty days showed much more complete degeneration. Degeneration is found to leave the facial nerve at the genu and to pass directly into the greater superficial petrosal nerve, the vidian nerve and the sphenopalatine ganglion. No degeneration could be followed over into the anastomosis on the internal carotid or into the pericarotid plexus.

Why did not the remaining seven cases show degeneration? In answer, one may point out that the nerves are small and the sections necessarily few, especially as several different methods were carried out for nerve fibers as well as for myelin. In fact, the three monkeys which showed positive results were the animals from which the sections were obtained in a satisfactory manner. These positive results were controlled by satisfactory negative results from nerves, not operated on, from the opposite side.

The failure to find degeneration in the internal carotid nerves may, of course, be due to technical inadequacy. But it seems to us more likely that the pathway to the carotid artery is interrupted in the small ganglia and in the scattered nerve cells which we have described in connection with the anastomosis. On the basis of analogy one might expect these internal carotid ganglia to provide postganglionic neurons at this point, as vasodilator fibers to other parts are interrrupted in the sphenopalatine ganglion probably and in the ganglia on the sublingual and submaxillary glands. These numerous nerve cells, grouped often in microscopic ganglia which might be called the internal carotid ganglia, provide the only large aggregate of ganglion cells in the course of these fibers. They could, then, easily assume this rôle. Further investigation of this point is desirable, however.

From an anatomic point of view, it seems fair to say that direct efferent nervous connection exists between the medulla oblongata and the carotid artery, and degeneration experiments as far as they go bear this demonstration out.

Afferent Fibers: The histologic structure of the internal carotid nerve, in monkeys, differs strikingly from that of the greater superficial

petrosal nerve. Apart from the unmyelinated and small myelinated nerve fibers, analogous to those found in the internal carotid nerve, the greater superficial petrosal nerve contains great numbers of large myelinated nerve fibers measuring about 10 microns in diameter. The majority of these large nerve fibers continue their course into the vidian nerve, and further through the sphenopalatine ganglion into some of its branches. Some of them, however, can be traced directly into the internal carotid nerve through the anastomosis already described. In the internal carotid plexus these fibers seem to pass both upward and downward on the artery (fig. 10).

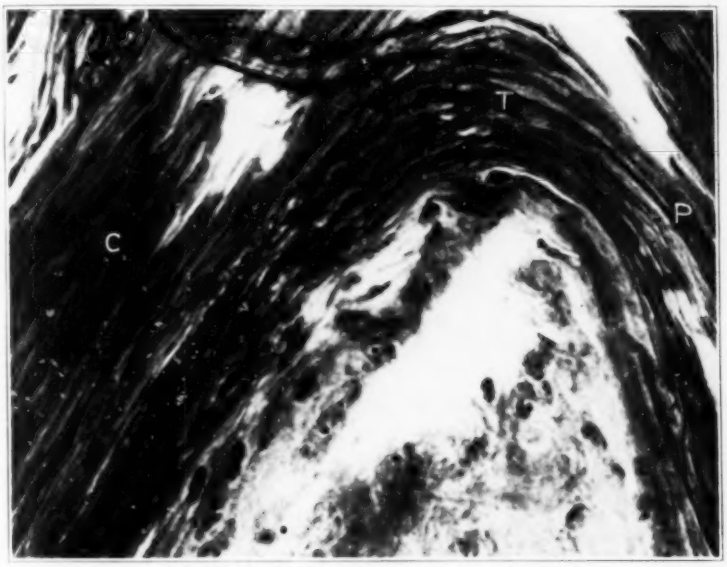

Fig. 10.—Large nerve fibers (*T*) passing from the greater superficial petrosal nerve (*P*) to the internal carotid nerve (*C*) of a Macacus rhesus monkey. Gross-Bielschowsky stain; × 682.

The fact, then, of the presence of these large myelinated nerve fibers in the internal carotid nerve (reported also by Ranson and Billingsley, 1918) raises the question as to their morphologic and functional significance. In order to determine this problem, we performed a number of experimental sections of the nerves under consideration, with the following results:

The majority of the small myelinated nerve fibers composing the internal carotid nerve arise from the superior cervical sympathetic ganglion. Their course can be followed into the vidian nerve as well as into the greater superficial petrosal nerves. In a central direction we have not studied them beyond the geniculate ganglion.

The large myelinated nerve fibers of the greater superficial petrosal nerve do not degenerate after removal of the superior cervical sympathetic ganglion. In only one of the five experiments was there a slight suggestion of degeneration of these large myelinated nerve fibers. After section of the facial nerve and nervus intermedius proximal to the geniculate ganglion, there was degeneration of few, if any, of these large myelinated fibers in the greater superficial petrosal. The removal of the sphenopalatine ganglion, done in one dog, was likewise without effect on these fibers, which is in conformity with the work of Prevost (1868). The large nerve fibers of the greater superficial petrosal do degenerate, on the other hand, when the greater superficial petrosal nerve is cut in the middle cerebral fossa, viz., distal to the geniculate ganglion.

The geniculate ganglion is now generally considered to be homologous to the cerebrospinal sensory ganglia. It would, therefore, follow, that these large myelinated fibers are cerebrospinal in nature and afferent in function. Yagita's (1914) observation that, after the vidian nerve is cut, some of the nerve cells in the geniculate ganglion degenerate points in the same direction. The suggestion, then, that the morphologically similar large myelinated nerve fibers passing from the greater superficial petrosal nerve into the internal carotid nerve represent cerebrospinal, afferent nerve fibers from the latter, becomes obvious.[3]

Unfortunately, we have not been able to follow these degenerating fibers in our sections through the anastomosis and on to the carotid artery. It seems likely that further efforts might well succeed, although the technical difficulties are great. It was observed that, after removal of the superior cervical sympathetic ganglion, large myelinated nerve fibers were found intact in the internal carotid nerve, while the small myelinated nerve fibers in this nerve were degenerated.

Moreover, it has been found that the section of the greater superficial petrosal nerve, in addition to the removal of the superior cervical sympathetic ganglion, produced complete degeneration of the nerve fibers in the internal carotid nerve. A few degenerating large myelinated nerve fibers were found in the satisfactory sections (fig. 12).

3. In one of our animals in which, in addition to an incomplete removal of the superior cervical sympathetic ganglion, the greater superficial petrosal nerve has been cut, distal to the geniculate ganglion, study of the sections stained with silver revealed the presence of bundles of nerve fibers passing from the greater superficial petrosal nerve into the dura mater. Some of the nerve fibers composing these bundles were degenerated. The afferent innervation of the dura mater by peripheral processes of nerve cells of the geniculate ganglion would thus represent a further widening of its sensory function (see *8* in fig. 11). See also W. Krause, as quoted by Henle and von Lenhossék.

Finally, although the evidence is not complete, it may be suggested that the large myelinated fibers on the internal carotid artery are afferent in function and pass through the greater superficial petrosal nerve to their own ganglion cells in the geniculate ganglion. These fibers would, therefore, correspond to other afferent fibers the cell station of which is in the geniculate ganglion (fig. 11). Moreover, such sensory innervation of cerebral vessels would be in conformity with the general conception of sensory innervation of blood vessels elsewhere.

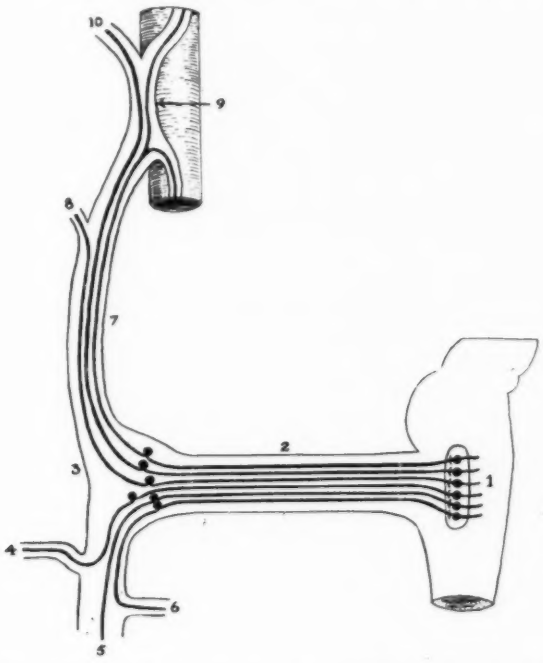

Fig. 11.—Diagram of afferent tracts, the ganglion cells of which are in the geniculate ganglion (*3*). *1* indicates the tractus solitarius; *2*, the nervus intermedius; *4*, taste and other afferent nerve fibers from the chorda tympani; *5*, deep sensibility from the face; *6*, cutaneous sensibility from the auricular zone of Ramsay Hunt; *7*, the greater superficial petrosal nerve; *8*, afferent nerve fibers from the dura mater; *9*, afferent nerve fibers from the internal carotid artery; *10*, afferent nerve fibers from the sphenopalatine ganglion distribution.

Physiology.—With the intention of studying the function of the nerve bundle, previously described, which connects the facial nerve with the internal carotid through the greater superficial petrosal nerve, the following experiments have been carried out.

All experiments were carried out on Macacus rhesus monkeys with the exception of two, in which cats were used. Anesthesia was obtained by the intraperitoneal injection of dial-Ciba, about 0.4 cc. per kilogram of body weight being used. Care was taken to reduce the dose as much as the animal's comfort would allow.

The technic of inserting a window in the skull for microscopic study of the vessels was that employed by Forbes (1928), and for the apparatus used we are indebted to Dr. Forbes, who presented us with an instrument set. The animal's head was held in position by a holder devised in our laboratory by Dr. Lyle Gage. This apparatus makes it possible to place the head in any position and to hold it there firmly by means of four pins, each of which impinges on the skull.

The microscope employed was equipped with 10x apochromatic objective and a K 10x ocular equipped with an eyepiece micrometer 0.5 mm. in length, subdivided fifty times. Thus the measurement of the vessels in question could be read in microns by multiplying the micrometer reading by a constant of 15. The source

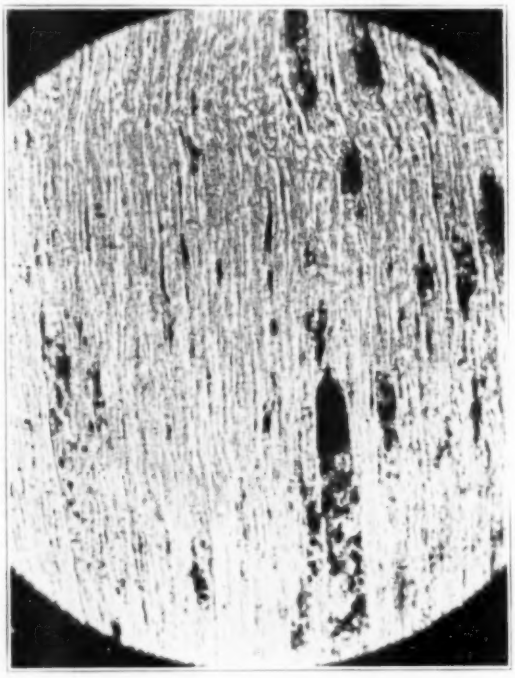

Fig. 12.—Degeneration of small, medium and large myelinated nerve fibers in the internal carotid nerve of a Macacus rhesus monkey. Herxheimer's stain; × 500.

of light was a Zeiss carbon arc lamp. Small platinum electrodes were used for stimulation of the nerves, with an induction coil attached to two dry cells. Bipolar stimulation was more frequeutly employed than unipolar.

A typical experiment with positive results is the following: A monkey (no. 4510), weighing 3.6 Kg., was given 1.6 cc. of dial-Ciba at the onset. A window was placed in the skull over the left parietal lobe, the dura being cut away and the surface of the pia irrigated beneath the window with Ringer's solution.

Suboccipital craniotomy was carried out to expose the facial nerve in the posterior fossa. A left temporal craniotomy was then carried out so as to expose the course of the greater superficial petrosal nerve as it crossed the floor of the middle cranial fossa.

Stimulation of the facial nerve was made twice for twenty seconds. In artery 1 (90 microns in diameter), no change was seen. Stimulation, when repeated on artery 2 (75 microns), resulted in a possible dilatation, too small, however, to be sure of. Stimulation of artery 3 (90 microns) for twenty seconds caused dilatation; the micrometer reading increased from 6 to 6.75. This was repeated three times with slight dilatation. Two further stimulations then produced no change.

The facial nerve was then sectioned close to the bulb, and the electrode was placed on the seventh and eighth nerves at their entrance into the internal auditory meatus. The same artery was observed, but at a somewhat different position. Each stimulation gave movement of the ipsolateral side of the face and a dilatation of the artery from a reading of 7 up to 8 on the micrometer, or at times from 7 to 7.5. The dilatation was usually maximum from fifteen to thirty seconds after the onset of stimulation, and came back to the initial diameter after from thirty to ninety seconds. Sponging of the nerves in the meatus (three occasions) produced an equally great dilatation.

The greater superficial petrosal nerve was then sectioned in its course across the middle fossa. After this, strong unipolar stimulation of the facial nerve produced no change in the vessel, although the facial muscles of the same side contracted as usual.

Stimulation of the peripheral portion of the greater superficial petrosal extradurally for thirty seconds gave an increase in the arterial reading from 7 to 8. This was repeated five times, with consistently the same result. As the anesthesia had become light, the animal struggled with each stimulus. The posterior root of the trigeminal nerve was touched; struggling resulted, but there was no change in the artery. This posterior root was then divided, after which stimulation of the greater superficial petrosal was done without struggling, but arterial dilatation took place as before. Tears had streamed from the eye on the side of the stimulation; there were none from that on the other side.

Two hours later, the stimulations were repeated with the same result; stimulation of the greater superficial petrosal nerve produced vasodilatation, and stimulation of the seventh nerve produced only facial movements.

Conclusion.—Stimulation of the facial nerve produces dilatation of certain pial arteries. Section of the greater superficial petrosal nerve puts an end to this reaction. Stimulation of the peripheral portion of the divided greater superficial petrosal produces energetic dilatation of the same artery.

Response of the facial muscles to stimulation of the seventh nerve is prompt and ceases instantly following cessation of stimulation, while the associated arterial dilatation lags behind the onset of stimulation and continues for a short time after its cessation.

A second experiment (monkey no. 4543) was carried out in exactly the same manner as the preceding one. The results were the same. Dilatation of certain (not all) arteries resulted from stimulation of the peripheral facial nerve, associated with movements of the face, salivation and production of tears. Section of the greater superficial petrosal stopped all effect from facial stimulation, and stimulation of the peripheral end of the former nerve caused dilatation of the cerebral arteries and the formation of tears.

The other similar experiments gave results comparable to those just described as far as they go. Two control operations were carried out on cats, one with

negative results; the other verified the findings of Forbes and Wolff (1928); i. e., stimulation of the cervical sympathetic chain peripherally produced constriction of the pial arteries on the same side. Afferent stimulation of the trunk of the vagus produced both ipsolateral and heterolateral arterial dilatation.

But there are many negative findings, due no doubt to technical difficulties, such as exposure of the facial and greater superficial petrosal nerves in their bony canals without injury of the nerve. The magnitude of the procedure also presented difficulties, each experiment lasting all day and sometimes on into the night. As the cranial cavity was usually opened in three places, the brain sometimes fell away from the window, making observation difficult or impossible.

In two monkeys the greater superficial petrosal nerve was exposed in the middle cranial fossa by removal of the temporal muscle, zygomatic process and temporal bone. In three monkeys the facial nerve and its branches were exposed by removal of the surrounding mastoid.

The results of these additional experiments were that in four animals, in which the greater superficial petrosal was stimulated, there was more or less convincing evidence of pial arterial dilatation in three cases. It was observed on several occasions that after section of the seventh nerve there was a tendency for the observed artery to vary spontaneously both in diameter and in outline. These changes seemed to be greater than might be expected from the fatigue of the preparation.

THE PERIVASCULAR NERVES OF THE PIAL AND INTRACEREBRAL VESSELS

The existence of vascular nerves of the pial vessels was long denied, but they were seen by a few earlier workers (von Kölliker, 1893; Gulland, 1898; Huber, 1899) and were completely described by Stöhr (Hassin, 1930). Nerves on the blood vessels in the medulla oblongata were described by Clarke (1929), and throughout the central nervous system by Penfield (1931).

This intracerebral perivascular plexus resembles that of the pial vessels (fig. 13), except that large bundles of nerves are found only in the pia. On intracerebral vessels there may be as many as from eight to a dozen fibers in company, but not more. Within the brain the perivascular nerves are small in caliber. There are many fine fibers, a fraction of a micron in diameter, and fewer larger fibers, about 2.5 microns in diameter. Thick and thin fibers on the pial vessels were described by Huber, who supposed the former to be always myelinated.

Within the brain the perivascular nerves are probably not myelinated. Our silver stain sometimes demonstrates a myelin sheath on the pial vessels, but never, so far, have we been sure of a myelin sheath on the intracerebral vascular nerves. A myelinated fiber within the pia has been found to lose its sheath as it continued downward on an intracerebral vessel (figs. 8 and 9 of Penfield, 1932).

In the anatomic study of the greater superficial petrosal nerve we have already traced the course of some of the nerve fiber elements by their size and sheaths, finding that the fibers of the internal carotid nerve are small and unmyelinated for the most part, although the myelinated fibers are also numerous but small. In the greater superficial petrosal nerve are many large myelinated fibers, which are thought to be afferent.

Fig. 13.—Myelinated nerve plexus on the basilar artery of a Macacus rhesus monkey. Weigert-Pal stain; × 200.

As the method we have used is a modification of the Gross-Bielschowsky silver technic,[4] we can study only the nerve fiber itself, although the sheath of Schwann is often indicated.

4. The technic involves dissecting the vessels from the substance of the nerve tissue with fine instruments and a dissecting microscope. The whole vessel is then carried through the staining solutions, and because of the selectivity of the stain is usually almost transparent so that the nerves can be followed about it with ease. For the procedure, see Penfield, W.: A Technique for Demonstrating the Perivascular Nerves of the Pia Mater and Central Nervous System, Am. J. Path., to be published.

The fact that large adventitial nerve endings, resembling Meissner's corpuscles (fig. 14), are found only on the pial vessels where they are appendages of large nerve fibers would indicate that afferent fibers are present only on the pial vessels. The only nerve endings we have so far encountered on the intracerebral vessels are very small structures shaped like a bunch of grapes and situated on or in the muscularis. These seem to be motor end-plates. There are, however, occasional coils of fibers that may also be considered end-organs of some sort.

An attempt was made to discover the origin of the intracerebral perivascular nerves on the basis of the separation of large and small fibers, but it was soon found that a thick fiber might give origin to a

Fig. 14.—Nerve ending resembling Meissner's corpuscle on the basilar artery of a Macacus rhesus monkey. Cajal's reduced silver method; × 401.

fine collateral branch (fig. 15). Indeed, the enormous number of collateral branches in T or Y shapes indicates that each parent ganglion cell may distribute its influence over a large territory, including many vessels.

We have seen no suggestion of the formation of a syncytium or a true net. That is, we have never seen a branch join itself or rejoin the parent fiber.

The innervation is seen to accompany arteries as small as 40 microns when flattened under the cover slip (but not smaller), which would mean a diameter of perhaps 25 or 30 microns when round. If the cerebral capillaries have a diameter of about 5 microns (Pfeifer, 1928), it is readily seen that there is a considerable body of dwindling arterial tube not accounted for. The arteries branch and rebranch after plunging

into the cerebral tissue and carry their nerve fibers with them like the tendrils of a vine, but no fibrils have been seen to go onto very small arteries.

This might be due to defects of the technic, but if these fibers have to do with the control of blood supply to areas of the brain, no further extension is necessary. There could be little effect from constriction or dilatation of smaller vessels than these, because of the enormous complexity of their branches and their widespread anastomoses with contiguous vessels. Wolff and Forbes (1928) found that pial vessels of from 110 to 340 microns best showed the constrictor action of

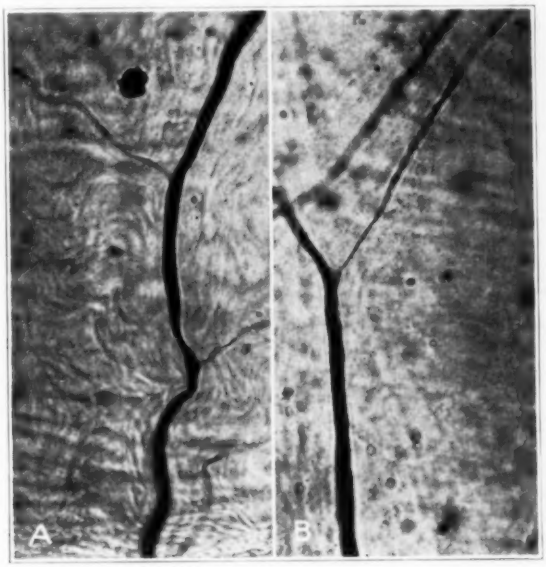

Fig. 15.—Large nerve fibers of a Macacus rhesus monkey giving rise to small collateral branches on the intracerebral vessels. Modified Gross-Bielschowsky method; *A*, × 875; *B*, × 1,200.

sympathetic stimulation, and we have observed vasomotor control only in pial arteries of 90 microns or more, although no careful study has been made of smaller arteries.

If the large pial arteries which carry nerve trunks intended for other vessels are left out of consideration, the nerve plexus present on the pial arteries of from 100 to 300 microns in diameter is much the same as the nerve plexus which accompanies these same arteries after they plunge at right angles into the brain, except that the myelinated fibers decrease or disappear and the pial sensory endings disappear from the intracerebral portion of the vessels.

It is, of course, impossible to observe the intracerebral arteries directly during life, but it would seem that because of their innervation they, like their pial parents, are capable of active response to vasomotor stimulation.

Effect of Sympathetic and Parasympathetic Nerve Section on the Vascular Plexus.—The sympathetic supply of the brain was removed first by excising the superior sympathetic ganglion and all nerve fibers from the internal carotid artery, and second, by removal of the stellate ganglion and all ganglia and fibers on the vertebral artery. We were greatly helped in the preparation and study of some of these animals by our colleague, Dr. Joseph Evans.

In a Macacus rhesus monkey, complete right-sided cerebral sympathectomy one hundred and seven days before autopsy resulted in our finding no nerve fibers on the common carotid, but the pial vessels of the right cerebral hemisphere presented normal perivascular nerves not differing from those of the opposite side. Nerves were plentiful on the right internal carotid in its intracranial portion and also on the middle and anterior cerebral arteries.

Fifty-three days after complete right sympathectomy in a Macacus rhesus monkey, the nerves were normal on pial and intracerebral vessels. Thirty-four days after the same operation on a cat, the perivascular nerves of the pial vessels appeared unaltered. Five days after complete removal of all sympathetic fibers to the cerebral vessels on both sides in another monkey, the pial vessels presented for the most part normal nerves, although there were irregular swellings on some nerve fibers. Ten days after right and left superior cervical sympathectomy, there were normal myelinated nerve fibers as well as unmyelinated ones on the anterior cerebral and large pial vessels, as shown by Weigert-Pal stains as well as by silver stains. Some questionable degeneration was present on the perivascular nerves of the left middle cerebral artery. In another experiment, eight days after complete right cervical sympathectomy of a Macacus rhesus monkey, only normal perivascular nerves could be found.

In five monkeys the superior cervical sympathetic ganglion and the greater superficial petrosal on the same side were removed. The time between operation and autopsy varied from fifty-one to four days. The silver staining, which was quite successful on both the pial and the intracerebral vessels, showed altogether normal perivascular nerves in three cases (figs. 16, 17 and 18). Of the other two, one showed degenerating large fibers on the pial vessels of the same side twelve days after sympathectomy and four days after section of the greater superficial petrosal nerve (fig. 19). The other case, forty-three and thirty-seven days after operation, showed both intracerebral and pial vessels with degenerating fibers on them. The degenerations were judged by silver stains only.

In two monkeys the seventh nerve was cut. In one case the vascular nerves appeared normal after thirty-two days. In the other, after eleven days, there were degenerating fibers on the pial vessels of the same side, and these abnormal fibers were all large ones like the degenerating fibers present in the greater superficial petrosal nerve.

These observations might be considered confusing. It must be remembered that the silver is capable of showing degeneration only if the fibers happen to be caught in the process of disintegration. But if

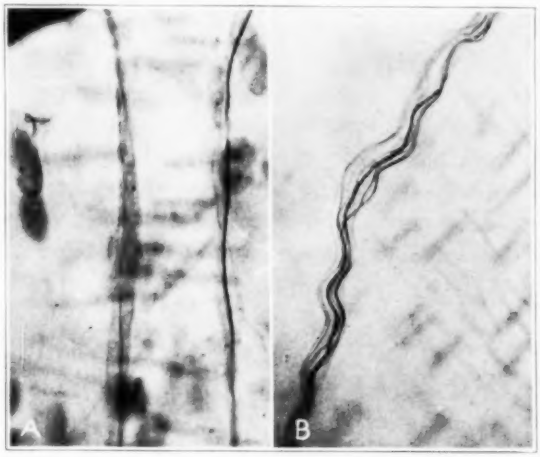

Fig. 16.—Intracerebral vascular nerves of a Macacus rhesus monkey fifty-one days after excision of the right superior sympathetic ganglion and forty-four days after section of the right greater superficial petrosal nerve. *A* shows the side of section; × 780. *B* shows the opposite side; × 444. Modified Gross-Bielschowsky stain.

Fig. 17.—Perivascular nerve, right basal ganglion, twenty-seven days after excision of the right superior sympathetic ganglion and nineteen days after section of the greater superficial petrosal nerve of a Macacus rhesus monkey. Modified Gross-Bielschowsky stain; × 444.

the silver shows normal nerve fibers after the time for degeneration has elapsed, one can only conclude with certainty, of course, that these remaining fibers have not been cut off from their proper ganglion cells.

It is, therefore, evident that only a small portion of the perivascular plexus is derived directly from the sympathetic or the greater superficial petrosal trunk. After section of the greater superficial petrosal nerve, there were definitely some abnormal fibers in two cases. These were large fibers which corresponded with the degenerating fibers within the nerve itself, and the same was true in one case in which section of the facial nerve was done.

Fig. 18.—Perivascular plexus of the right carotid artery after ipsolateral sympathectomy and parasympathectomy. Note the large and small nerve fibers. From the same case as the section in figure 19, with the same stain; × 750.

Much careful work is yet to be done to verify and extend this work, but certain conclusions are evident. Either the majority of nerve fibers on the pial and intracerebral blood vessels are derived from nerves other than the greater superficial petrosal and the cervical sympathetic nerves, or there are cell stations in the course of these two innervations which interrupt the final nervous pathway. It has been shown from time to time that various cranial nerves send twigs to the pia mater. Yet there is nothing constant about this innervation, and stimulation of the other cranial nerves does not produce physiologic change in the pial vasculature, as was pointed out by Cobb and Finesinger.

Ganglion cells are present in the anastomosis of the greater superficial petrosal nerve with the internal carotid nerve. These probably serve to interrupt the fibers of the greater superficial petrosal nerve wholly or in part in their passage to the carotid artery. This is to be expected by analogy, as the sphenopalatine ganglion interrupts the vasodilator fibers for the nasal cavities. There are also (rather rare) ganglion cells scattered along the pial vessels and occasionally an accessory macroscopic sympathetic ganglion on the carotid artery in its canal within the cranium (fig. 20). This was true in one of four dissections made by us on human beings.

Fig. 19.—Degenerating large fibers on the pial artery four days after section of the greater superficial petrosal nerve and twelve days after sympathectomy in a Macacus rhesus monkey. The small fibers are normal. Note the collateral branching. Modified Gross-Bielschowsky stain; × 1,240.

The most likely conclusion is that both sympathetic and parasympathetic innervations are interrupted in their course on the vessels by synapses. This interruption might be carried out by relatively few ganglion cells because of the enormous amount of collateral branching found in the final nerve fibers. Such scattered ganglion cells and microscopic ganglia do exist, as described in the preceding paragraph.

SUMMARY

There is a pathway for efferent impulses from the medulla oblongata to the cerebral vessels (fig. 21). Electrical stimulation at any point on

this pathway produces dilatation of the arteries of the pia mater. This innervation is antagonistic, in its action on these arteries, to that of the cervical sympathetic trunk. It may, therefore, be termed parasympathetic. This parasympathetic pathway in monkeys forms the efferent limb of a reflex arc. The afferent limb of the arc is found in the vagus of the same or opposite side.

From an anatomic point of view we have demonstrated a bundle of small myelinated and nonmyelinated fibers which may be recognized as a distinct portion of the nervus intermedius of Wrisberg just proximal to the geniculate ganglion. This bundle passes directly into the greater

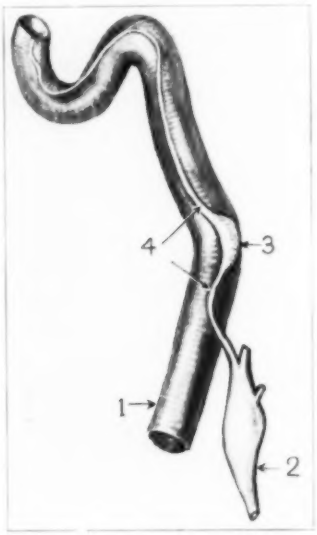

Fig. 20.—Accessory sympathetic ganglion on the internal carotid artery of man, after actual dissection. *1* indicates the internal carotid artery; *2*, the superior cervical sympathetic ganglion; *3*, the accessory sympathetic ganglion; *4*, the internal carotid nerve.

superficial petrosal nerve without interruption in the ganglion. Further along the nerve a distinct bundle of nerve fibers emerges from the greater superficial petrosal nerve to the plexus of nerves on the internal carotid.

After section of the facial nerve, degeneration may be followed outward past the geniculate ganglion and through the greater superficial petrosal to the anastomosis of this nerve with the internal carotid nerve. There are a constant small ganglion here and scattered ganglion cells in the anastomosis. It seems likely that the fibers of the tract are interrupted by synapses at this point. After section of the greater superficial petrosal nerve, the axons of the perivascular cerebral nerves

show scattered evidence of degeneration. It is suggested that these may be afferent fibers from pial vessels through the greater superficial petrosal nerve.

Experimentation showed that in monkeys section of the greater superficial petrosal nerve prevented dilatation of the cerebral arteries in response to facial stimulation, while peripheral stimulation of the greater superficial petrosal nerve continued to cause arterial dilatation.

We have further noted in several cases that section of the seventh or greater superficial petrosal nerve resulted in recurring spontaneous variations in arterial caliber.

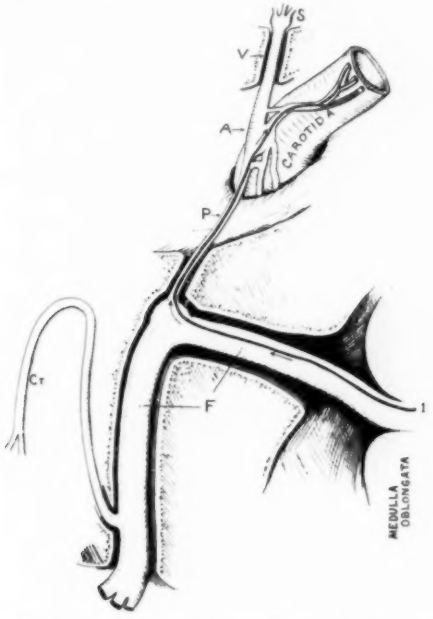

Fig. 21.—Diagram of the vasodilator nerve fibers for the cerebral blood vessels (*1*). *F* indicates the facial nerve; *P*, the greater superficial petrosal nerve; *A*, anastomosis of the greater superficial petrosal nerve with the internal carotid nerve; *V*, the vidian nerve; *S*, the sphenopalatine ganglion; *C.t.*, the chorda tympani.

The perivascular nerves of the pial vessels and also the continuation of these nerves on the large and medium-sized intracerebral arteries (but not on the small arteries) are described. Small nerve endings resembling motor end-plates are found on the intracerebral arteries, suggesting that they too may be capable of the contraction and dilatation which can be demonstrated by direct observation only in the case of the pial arteries.

Complete removal of all sympathetic nerve fibers which enter the cranial cavity on the carotid and vertebral arteries does not appreciably

reduce the number of normal intracranial perivascular nerve fibers. Degeneration, as judged by axon stains, is occasionally found within the first month after sympathectomy, which suggests that a small number of sympathetic fibers do reach the pial vessels directly.

When *both greater superficial petrosal and sympathetic nerves are removed*, the pial and intracerebral vessels are still found to be richly supplied with nerve fibers. It becomes evident, therefore, that it is not possible to denervate the cerebral vessels by removing both sympathetic and parasympathetic innervation.

It is suggested that the parasympathetic pathway is interrupted by synapses, with scattered ganglion cells, just before reaching the internal carotid artery, and that the cervical sympathetic chain, which has been thought to have its postganglionic stations in the superior sympathetic, may also be interrupted by the scattered ganglion cells along the course of the internal carotid and cerebral arteries.

The occasional branches to the pia from other cranial nerves, reported by Stöhr and others, hardly seem numerous enough to be important, but this source deserves further investigation.

The extraordinary amount of collateral branching of axons of the cerebral perivascular nerves indicates that one ganglion cell must innervate a large segment of the vascular tree.

ABSTRACT OF DISCUSSION

Dr. Peter Bassoe, Chicago: It occurred to me that this work may explain the mechanism of the vasodilator phenomenon that I have had occasion to observe in two patients during the last six months.

The first patient was a woman who had had an abscess of the parotid gland four years previously. Partial facial paralysis complicated by spasm developed. One year ago, three years after the operation, the following phenomenon developed, which has been constant ever since: Whenever she begins to eat, particularly sour substances, she experiences a feeling of heat in the external ear and the adjoining part of the cheek and these parts become red and then perspiration sets in.

I have tested this many times, and have also found that I could produce the sensation of heat and the redness, but not the perspiration, by applying sour and salty substances to the posterior third of the tongue, and not to the anterior third.

The second patient was a man who had had a mixed tumor of the parotid gland removed. This was followed by complete facial paralysis, with no spasm.

Quite a large number of such cases have been reported, nearly all from Russia and Poland, the reason being that abscess of the parotid gland is a common complication of typhus fever, which is prevalent in those countries. The phenomenon described is known as the "auriculotemporal syndrome."

Dr. Israel Strauss, New York: In many physiologic and other experiments with nervous structures I have noticed that it is possible to do them 100 times and obtain 100 positive results. I wish Dr. Cobb and Dr. Finesinger would explain to me why they did the experiment with the vagus 133 times, I think it was, and 25 times obtained no reaction. It seems to be a fairly large percentage of negative reactions.

DR. STANLEY COBB: I would answer Dr. Strauss by referring to the experiments. In them we almost always had the animals under anesthesia. In later experiments, however, we learned how to operate under local anesthesia. When using a great deal of amytal, we had less response to stimulation. Moreover, there was a great deal of operating to be done; often we would have to operate all morning and after lunch start on the experiment. When an animal went into shock, there would be little or no response to stimulation. These animals were discarded. In other words, we must have a reactive animal to start with; these reactions are variable, showing a dilatation of the artery of from 8 to 60 per cent of the diameter, depending on the condition of the animal, shock, depth of anesthesia and the like.

I should like to emphasize here that there is an innervation of the arteries of the brain like the innervation of other arteries of other organs. There is a sympathetic and an opposed parasympathetic reactivity, just as one would expect. Hill, in 1898, said that there was no innervation of the pial arteries; this has been handed down as a fact from textbook to textbook.

I might add a few comments on the work. In all of our experiments we have had the window in the occipitoparietal region, examining the arteries overlying only one area of cortex. This area, according to our experiments, has both a sympathetic and a parasympathetic innervation, the latter following the course we have described with Penfield and Chorobski.

We have no data on what the innervation of the arteries of the base of the brain or of the hind brain may be. We must have more experiments on that point. I suspect there may be an innervation along the vertebral arteries. Our work is in that way incomplete.

I might add that although these experiments were started and planned in unison with Dr. Penfield and Dr. Chorobski, afterward we worked for about eight months absolutely independently. At the end of that time I wrote up my results and sent them to Montreal. I received a letter within a week from Penfield; our independent results were so similar that I was as startled as Penfield was.

DR. WILDER PENFIELD: I am much interested in Dr. Bassoe's question. Of course, the parotid gland is not innervated by the facial nerve. This nerve supplies the sublingual and submaxillary glands. On the other hand, the glossopharyngeal nerve innervates the parotid gland, and also gives sensory fibers to the posterior one third of the tongue. It is, therefore, reasonable to assume that a reflex might be initiated through the afferent fibers arising in the posterior one third of the tongue and produce vasodilatation within the parotid gland, as this nerve carries both dilator fibers and secretory fibers to that gland.

BIBLIOGRAPHY

Arnold, Friedrich: Handbuch der Anatomie des Menschen, Freiburg im Breisgau, A. Emmerling und Herder, 1851, vol. 2.

Barcroft, J.: The Respiratory Function of the Blood, New York, Cambridge University Press, 1914.

Bayliss, W. M.: On the Origin from the Spinal Cord of the Vasodilator Fibers of the Hind Limb and on the Nature of These Fibers, J. Physiol. **26**:173, 1901.

Further Researches on Antidromic Nerve Impulses, ibid. **28**:276, 1902.

The Vasomotor System, New York, Longmans, Green & Co., 1923.

Bernard, Claude: Leçons sur la physiologie et la pathologie du système nerveux, Paris, J. B. Baillière et fils, 1858.

Blier, Z.: Physiology of the Sphenopalatine Ganglion, Am. J. Physiol. **93**:398, 1930.

Bruce, A. N.: Vasodilator Axone Reflexes, Quart. J. Exper. Physiol. **6**:339, 1913.

Carpenter, F.: On the Histology of the Cranial Autonomic Ganglia of the Sheep, J. Comp. Neurol. **22**:447, 1912.

Clarke, S.: Innervation of the Blood Vessels of the Medulla and Spinal Cord, J. Comp. Neurol. **48**:247, 1929.

Cobb, S.: The Relationship of the Cervical Sympathetic Nerves to the Cerebral Blood Supply, Am. J. M. Sc. **178**:528, 1929.

Fofanow, L. L., and Tschalussow, M. A.: Ueber die Beziehungen des Nervus depressor zu den vasomotorischen Zentren, Arch. f. d. ges. Physiol. **151**:543, 1913.

Forbes, H. S., and Wolff, H. G.: Cerebral Circulation: III. The Vasomotor Control of Cerebral Vessels, Arch. Neurol. & Psychiat. **19**:1057 (June) 1928.

Gaskell, W. H.: Do the Nervi Erigentes Leave the Spinal Cord in Anterior or Posterior Roots? J. Physiol. **8**:iv, 1887.

The Involuntary Nervous System, New York, Longmans, Green & Co., 1920.

Gulland, L.: The Occurrence of Nerves on Intracranial Blood Vessels, Brit. M. J. **2**:781, 1898.

Hassin, G. B.: The Nerve Supply of the Cerebral Blood Vessels in the Vegetative Nervous System, Baltimore, Williams & Wilkins Company, 1930, chap. 19, p. 437.

Heidenhain, R.: Ueber die Wirkung einiger Gifte auf die Nerven der Glandula submaxillaris, Arch. f. d. ges. Physiol. **5**:309, 1872.

Henle, F. G. J.: Handbuch der systematischen Anatomie des Menschen, Braunschweig, F. Vieweg & Sohn, 1868, vol. 3, pt. 1.

Herrick, C. J.: An Introduction to Neurology, Philadelphia, W. B. Saunders Company, 1924.

Hill, L.: The Mechanism of the Circulation of the Blood, in Schäfer, E. A.: Text-Book of Physiology, Edinburgh, Y. J. Pentland, 1900, vol. 2, p. 1.

Huber, G. C.: Observations on the Innervation of the Intracranial Vessels, J. Comp. Neurol. **9**:1, 1899.

Johnston, J. B.: The Nervous System of Vertebrates, Philadelphia, P. Blakiston's Son & Co., 1906.

Kölliker, Albert: Handbuch der Gewebelehre des Menschen, Leipzig, Wilhelm Engelmann, 1893.

Krause, W., quoted by Henle.

Krogh, August: Anatomie und Physiologie der Capillaren, Berlin, Julius Springer, 1924.

Landolt, H.: Ueber die Innervation der Thränendrüse, Arch. f. d. ges. Physiol. **98**:189, 1903.

Langley, J. N.: The Sympathetic and Other Related Systems of Nerves, in Schäfer, E. A.: Textbook of Physiology, Edinburgh, Y. J. Pentland, 1900, vol. 2, p. 616.

Lassell, O., and Fenton, R.: The Embryology and Neurohistology of Sphenopalatine Ganglia Connections: A Contribution to the Study of Otalgia, Laryngoscope **38**:371, 1928.

Lenhossék, Michael: Das Ganglion geniculi nervi facialis und seine Verbindungen, in Beiträge zur Histologie des Nervensystems und der Sinnesorgane, Munich, J. F. Bergmann, 1894, p. 147.

Ueber das Ganglion sphenopalatinum und den Bau der sympathischen Ganglion, ibid., p. 163.

Martin, E. G., and Mendelhall, W. L.: The Response of the Vasodilator Mechanism to Weak, Intermediate and Strong Sensory Stimulation, Am. J. Physiol. **38**:98, 1915.

Müller, L. R., and Dahl, W.: Die Beteiligung des sympathischen Nervensystems an der Kopfinnervation, Deutsches Arch. f. klin. Med. **99**:48, 1910.

Penfield, W.: Intracerebral Vascular Nerves, Arch. Neurol. & Psychiat. **27**:30 (Jan.) 1932.

Penzo, R.: Ueber das Ganglion geniculi und die mit demselben zusammenhängende Nerven, Anat. Anz. **8**:738, 1893.

Pfeifer, R. A.: Die Angioarchitektonik der Grosshirnrinde, Berlin, Julius Springer, 1928.

Pieschel, C.: De parte cephalica nervi sympathici in equo prodromus, Leipzig, E. Stange, 1844; quoted by Arnold.

Ramón y Cajal, S.: Histologie du système nerveux de l'homme et des vertèbres, Paris, A. Maloine, 1911.

Ranson, S. W.: The Anatomy of the Nervous System, ed. 4, Philadelphia, W. B. Saunders Company, 1931.

——and Billingsley, P. R.: The Conduction of Painful Afferent Impulses in the Spinal Nerves, Am. J. Physiol. **40**:571, 1916.

Rauber, A. A., and Kopsch, F.: Lehrbuch der Anatomie des Menschen, ed. 8, Leipzig, Georg Thieme, 1909, pt. 1.

Retzius, G.: Untersuchungen über die Nervenzellen der cerebro-spinalen Ganglien und der übrigen peripherischen Kopfganglien, mit besonderer Rücksicht auf die Zellenausläufer, Arch. f. Anat. u. Entwcklngsgesch., 1880, p. 369.

Rhinehart, S.: The Nervus Facialis of the Albino Mouse, J. Comp. Neurol. **30**:81, 1918.

Sherrington, C. S., quoted by Hill.

Speranskaja-Stepanowa, E. N.: Postganglionare sympathetische vasoconstrictorische und vasodilatorische Axonreflexe, Arch. f. d. ges. Physiol. **210**:633, 1925.

Stavraky, G. W.: The Effect on the Submaxillary Gland of Stimulation of the Partly Degenerated Sympathetic Nerve, Quart. J. Exper. Physiol. **21**:123, 1931.

Stöhr, P., Jr.: The Nerves of the Blood Vessels, the Heart, the Meninges, Digestive Tract and Urinary Bladder, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932.

Streeter, G., in Keibel, Franz, and Mall, F. P.: Manual of Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, vol. 2.

Talbott, J. H.; Wolff, H. G., and Cobb, S.: The Cerebral Circulation: VII. Changes in Cerebral Capillary Bed Following Cervical Sympathectomy, Arch. Neurol. & Psychiat. **21**:1102 (May) 1929.

Tschalussow, M. A.: Die Innervation der Gefässe der Nasenschleimhaut, Arch. f. d. ges. Physiol. **151**:523, 1913.

Undritz, W.: Ueber vasomotorische Reflexe der Nase, Ztschr. f. Hals-, Nasen- u. Ohrenh. **25**:157, 1930.

Vulpian, A.: Expériences ayant pour but de determiner la véritable origine de la corde du tympan, Compt. rend. Acad. d. sc. **86**:1053, 1878.

Weigner, K.: Ueber den Verlauf des Nervus intermedius, Anat. Hefte **28**:97, 1905.

Wilder, H. H.: The History of the Human Body, ed. 2, New York, Henry Holt & Company, 1923.

Winslow, J. B.: An Anatomical Exposition of the Structure of the Human Body, ed. 3, translated from the French by G. Douglas, Edinburgh, A. Donaldson, 1749.

Yagita, R.: Einige Experimente an dem Nervus petrosus superficialis major zur Bestimmung des Ursprungsgebiete des Nerven, Folia neurobiol. **8**:361, 1914.

CEREBRAL CIRCULATION

XVIII. EFFECT OF CAFFEINE ON CEREBRAL VESSELS

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Survey of the Literature
1. Effect on Amphibians
2. Effect on Mammals
   (*a*) Size of Blood Vessel
   (*b*) Blood Pressure
   (*c*) Heart Rate
   (*d*) Autonomic Nervous System
Original Experiments
1. Experiments During Amytal Anesthesia
   (*a*) Effects After Intravenous Administration
   (*b*) Effects After Local Administration
2. Experiments During Ether Anesthesia
   (*a*) Effects After Intravenous Administration
   (*b*) Effects After Local Administration
3. Experiments After Recovery from Ether Anesthesia
   (*a*) Effects After Intravenous Administration
   (*b*) Effects After Local Administration
4. Effects of Caffeine on Animals with Low Blood Pressure
   (*a*) Experiments During Amytal Anesthesia
Comment
Summary

SURVEY OF THE LITERATURE

The effect of caffeine and its compounds on circulatory phenomena has long been of interest to physiologists, pharmacologists and clinicians. Since the isolation of the drug in 1820 by Runge, research has piled on research, until at present the literature is extensive. Stuhlman and Falck [1] not only mentioned this fact, but enumerated fifty-one articles published between 1820 and 1856. Most of the study has been centered on the effect of coffee, caffeine and oil of coffee on the pulse rate, blood pressure, respiration, kidney action and nerve excitability;

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1. Stuhlman, J., and Falck, C. P.: Virchows Arch. f. path. Anat. **11**:324, 1857.

more recently, emphasis has been on the osmotic pressure, gaseous content and blood, and on the cardiac output; within the last year the effect of caffeine on cerebrospinal fluid pressure has been studied.

1. *Effect on Amphibians.*—In the frog it has been found that caffeine has a direct action on the blood vessel or its nerve ending, in most cases causing dilatation (Amsler and Pick [2] and Heubner [3]). Sandor [4] found that a weak solution of caffeine, when directly applied, caused a contraction of the capillaries in the base of the brain, the tongue and muscle. Greater concentrations on the base of the brain caused an increase in blood flow with dilatation of all the blood vessels. Very weak solutions of caffeine caused a slight contraction of the capillaries followed by dilatation. This action was not at all consistent. Caffeine has a direct action on the heart muscle (Johannsen,[5] Beyer,[6] Heathcote [7] and Roth [8]). Small doses increased the rate and force of the heart beat (Beyer, Johannsen, Heathcote and Barbour and Kleiner [9]), the degree of contraction even after electrical stimulation and the arterial blood pressure (Beyer).[6] The increase is often followed by a slowing of the heart rate (Johannsen [5] and Stuhlman and Falck [1]). Very large doses diminish the rate of the heart beat and decrease the blood pressure (Beyer [6]). Barbour and Kleiner [9] showed that the cardiac action of caffeine was due to two factors: (1) the depression of the vagus endings of the heart, and (2) irritability of the cardiac muscle. Small doses of caffeine in the frog cause a rise in blood pressure, while large doses cause a drop. The evidence for the effect of caffeine on the vasomotor centers of the medulla in the frog and turtle is not conclusive (Bush [10]).

2. *Effect on Mammals.*—(*a*) Size of Blood Vessel: Most investigators found that caffeine caused a vasodilatation in various parts of the body. This has been found in the kidney by oncometric measurements and perfusion experiments (von Schroeder,[11] Munk,[12] Albanese,[13]

2. Amsler, C., and Pick, E. P.: Arch. f. exper. Path. u. Pharmakol. **85**:61, 1919.

3. Heubner, W.: Klin. Wchnschr. **2**:2015, 1923.

4. Sandor, G.: Arch. f. d. ges. Physiol. **213**:492, 1926.

5. Johannsen, O.: Ueber die Wirkungen des Kaffein, Dorpat, H. Laakmann, 1869; quoted by Sollmann, T.: A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology, Philadelphia, W. B. Saunders Company, 1930.

6. Beyer, H. G.: Am. J.M.Sc. **2**:71, 1885.

7. Heathcote, R. St. A.: J. Pharmacol. & Exper. Therap. **16**:327, 1920.

8. Roth, G. B.: J. Pharmacol. & Exper. Therap. **30**:321, 1927.

9. Barbour, H. G., and Kleiner, S. B.: J. Pharmacol. & Exper. Therap. **7**: 541, 1915.

10. Bush, A. D.: J. Pharmacol. & Exper. Therap. **14**:313, 1919.

11. von Schroeder, W.: Arch. f. exper. Path. u. Pharmakol. **24**:85, 1887.

12. Munk, I.: Virchows Arch. f. path. Anat. **107**:291, 1889.

13. Albanese, M.: Arch. f. exper. Path. u. Pharmakol. **33**:449, 1895.

Schlayer and Hedinger [14] and Sollmann and Pilcher [15]). It has also been found in the spleen and vessels of the skull (Philips and Bradford [16]), the splanchnic organs (Albanese [17] and Gottlieb and Magnus [18]), the intestine (Loewi, Fletcher and Henderson [19]) and the liver (Berezin [20]). It has been demonstrated in the renal vessels (Schlayer and Hedinger [14] and Cow [21]) and the splenic vessels (Cow [21]). In the visceral vessels (Morimoto [22]) often the dilatation is preceded by a slight constriction of brief duration, which has been found in the kidney (Philips and Bradford [16]), intestines (Beco and Plumier [23]), lung (Berezin [24]) and vessels of the ear (Eskin [25]). Morimoto [22] alone found a slight constriction in the kidney vessels with the use of small doses of caffeine. Caffeine caused dilatation in the cerebral vessels in animals (Wiechowsky [26] and Hirschfelder [27]) and in the retinal vessels (Hirschfelder [27]). Roy and Sherrington [28] found an initial expansion, followed by a slight contraction of brain volume, which in turn was followed by a well marked expansion. Raphael and Stanton [29] found no change in brain volume in human beings after caffeine. Stevenson, Christensen and Wortis [30] and Denkers [31] found a decrease in cerebrospinal fluid pressure in forty-nine of fifty patients, which was interpreted as due to a vasoconstriction. The evidence in animal experimentation points

14. Schlayer and Hedinger, Deutsches Arch. f. klin. Med. **90**:1, 1907.

15. Sollmann, T., and Pilcher, J. D.: J. Pharmacol. & Exper. Therap. **3**:19, 1911-1912.

16. Philips, C. D. F., and Bradford, J. R.: J. Physiol. **8**:117, 1887.

17. Albanese, M.: Arch. f. exper. Path. u. Pharmakol. **43**:305, 1900.

18. Gottlieb, H., and Magnus, R.: Arch. f. exper. Path. u. Pharmakol. **45**:223, 1901.

19. Loewi, O.; Fletcher, W. M., and Henderson, D. E.: Arch. f. exper. Path. u. Pharmakol. **53**:15, 1905.

20. Berezin, W. E.: Action of Poisons on the Vessels of the Liver, Russk. Vrach **13**:805, 1914; abstr., J. A. M. A. **63**:1989 (Nov. 28) 1914.

21. Cow, D.: J. Physiol. **42**:125, 1911.

22. Morimoto, M.: Ztschr. f. Kreislaufforsch. **21**:324, 1929.

23. Beco and Plumier: J. de physiol. et de path. gén. **8**:10, 1906.

24. Berezin, V. I.: Action of Poisons on the Vessels in the Lungs, Russk. Vrach **13**:289, 1914; abstr., J. A. M. A. **63**:364 (July 25) 1914.

25. Eskin, D. A.: Action of Poisons on the Vessels of Inflamed Tissues, and of Epinephrin in Peritonitis, Russk. Vrach **13**:809, 1914; abstr., J. A. M. A. **63**:1989 (Nov. 28) 1914.

26. Wiechowsky, W.: Arch. f. exper. Path. u. Pharmakol. **48**:376, 1902.

27. Hirschfelder, A. D.: J. Pharmacol. & Exper. Therap. **6**:597, 1915.

28. Roy, C. S., and Sherrington, C. S.: J. Physiol. **11**:85, 1890.

29. Raphael, T., and Stanton, J. M.: The Action of Certain Drugs on Brain Circulation in Man, Arch. Neurol. & Psychiat. **2**:389 (Oct.) 1919.

30. Stevenson, L.; Christensen, B. E., and Wortis, S. B.: The Intracranial Pressure in Health and Disease, Baltimore, Williams & Wilkins Company, 1929, vol. 8, p. 130.

31. Denkers, P. G.: Am. J. M. Sc. **181**:675, 1931.

definitely in the direction of vasodilatation, often preceded by a slight transient vasoconstriction. The results of Stevenson, Christensen and Wortis and Denkers will be discussed later.

(*b*) Blood Pressure: In mammals, some of the earlier investigators (Leven,[32] Binz,[33] Wagner,[34] Wiechowsky,[26] Reichert[35] and Vinci[36]) found a rise in blood pressure after the administration of caffeine intravenously or subcutaneously. It was noted that the rise in blood pressure was greater if the initial blood pressure was low (Santesson[37]). This was found to be true after the destruction of the medulla (Reichert[35] and Swirski[38]), repeated hemorrhage or inanition (Vinci[36]). Pearce, Hill and Eisenbrey[39] found a rise in blood pressure after arsenic. Other investigators (Aubert,[40] Maki,[41] von Schroeder,[42] Philips and Bradford,[16] Vinci,[36] Gottlieb and Magnus[18] and Loewi, Fletcher and Henderson[19]) found a definite drop in blood pressure after caffeine. The drop was proportional to the amount of caffeine used (Aubert[40]), and was found most generally after intravenous and intraperitoneal (von Schroeder[42]) administration. It was not found after subcutaneous injection of small doses (Philips and Bradford[16]), but was present after the subcutaneous injection of large doses. It was found after chloral and atropine (Maki[41]). The drop in blood pressure went together with the rise in the oncometric reading (Philips and Bradford,[16] Gottlieb and Magnus[18] and Loewi, Fletcher and Henderson[19]). Diuresis took place in the presence of a falling blood pressure (von Schroeder),[42] but ceased when the blood pressure was too low. When fluid is introduced slowly, there is a small initial rise of blood pressure due to the administration of fluid (Sollmann and Pilcher).[15] This is followed by a drop in blood pressure, indicating cardiac depression. Oncometric readings showed a rise that implied vasodilatation. The best evidence in experimental animals, under various anesthesias, indicates that the acute effect of caffeine in small and moderate doses is a slight rise in the blood pressure curve. Large

32. Leven, M.: Arch. de physiol. norm. et path. **1**:179, 1868.

33. Binz, V. C.: Arch. f. exper. Path. u. Pharmakol. **9**:31, 1878.

34. Wagner: Dissertation, Berlin, 1885; quoted by Swirski, G.: Arch. f. d. ges. Physiol. **104**:260, 1904.

35. Reichert, E. T.: Therap. Gaz. **6**:294, 1890.

36. Vinci, G.: Arch. di farmacol. sper. **3**:385, 1895.

37. Santesson, G. C.: Skandinav. Arch. f. Physiol. **12**:259, 1902.

38. Swirski, G.: Arch. f. d. ges. Physiol. **104**:260, 1904.

39. Pearce, R. M.; Hill, M. C., and Eisenbrey, A. B.: J. Exper. Med. **12**:200, 1910.

40. Aubert, H.: Arch. f. d. ges. Physiol. **5**:589, 1872.

41. Maki: Inaug. Diss., Strassbourg, 1884; quoted by Sollmann, T.: A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology, Philadelphia, W. B. Saunders Company, 1930.

42. von Schroeder, W.: Arch. f. exper. Path. u. Pharmakol. **22**:39, 1886.

intravenous doses cause a drop in the blood pressure reading, the result of cardiac depression. The lasting effects of small doses seem to be to keep the blood pressure slightly above its normal value. Large doses cause a persistent drop in blood pressure.

(*c*) Heart Rate: The effect of caffeine on the heart rate depends on the dose used. Very small doses hypodermically had no effect on the heart rate (Wagner [34] and Smith, Miller and Graber [43]). Small and moderate doses hypodermically and intravenously primarily caused an acceleration in rate (Leven,[32] Johannsen,[5] Aubert,[40] Philips and Bradford,[16] Hare and Marshall,[44] Hedborn,[45] Bock,[46] Reichert,[35] Cushny and van Naten [47] and Swirsky [38]), which in turn is followed by a decrease in rate (Leven,[32] Johannsen,[5] Philips and Bradford,[16] Hare and Marshall,[44] Hedborn,[45] Bock,[46] Reichert [35] and Cushny and van Naten [47]). Large doses in most cases cause an acceleration (Johannsen [5]) followed by a decrease, the decrease being greater as the dosage is increased (Johannsen,[5] Philips and Bradford,[16] Hare and Marshall [44] and Reichert [35]). Larger doses cause a cardiac arrhythmia (Wagner [34] and Cushny and van Naten [47]), and often the heart is arrested in diastole (Hare and Marshall [44]). Some of the earlier workers (Leven [32] and Johannsen [5]) found that these effects were the same after division of the vagus and sympathetic in the neck and after section of the vagus and the administration of atropine, and concluded that the effect was due to the drug acting directly on the heart. In support of this, Hedborn [45] found that when blood containing caffeine was passed through the coronary arteries in the excised mammalian heart, the pulse was accelerated and the amplitude of the contraction increased. Cushny and van Naten [47] showed that all of the effects could be explained by the action of the drug on the excitomotor center and on the heart muscle. There has been some evidence that the slowing is due to the stimulation of the vagus center in the medulla (Wagner [34] and Bock [46]), but this has not been conclusive.

(*d*) Autonomic Nervous System: The effects of caffeine on the autonomic nervous system are not clear, in spite of the considerable experimental work. Most of the evidence suggests that caffeine acts centrally and peripherally. It acts as a mild stimulant on the central sympathetic (von Schroeder,[42] Sollmann and Pilcher [48] and Watanabe [49])

43. Smith, F. M.; Miller, G. H., and Graber, V. C.: J. Clin. Investigation **2**:157, 1926.

44. Hare and Marshall: Philadelphia M. News **52**:337, 1888.

45. Hedborn, K.: Skandinav. Arch. f. Physiol. **9**:1, 1899.

46. Bock, J.: Arch. f. exper. Path. u. Pharmakol. **43**:367, 1899.

47. Cushny, A. R., and van Naten, B. K.: Arch. internat. de pharmacodyn. et de thérapie **9**:169, 1901.

48. Sollmann, T., and Pilcher, J. D.: Am. J. Physiol. **26**:233, 1910.

49. Watanabe, M.: Tohoku J. Exper. Med. **10**:177, 1928.

and also on the central vagus mechanism (Wagner [34] and Reichert [35]). Peripherally, it acts as a paralysant of the sympathetics in many ways. Caffeine inhibits the reaction of the accelerator fibers in the anneau de Vieussens (Fredericque [50]) and the glycosuria caused by epinephrine (Bardier, LeClerc and Stillmunkes [51]). It reduces the hypertension due to splanchnic stimulation (Bardier, Duchein and Stillmunkes [52]) and the action of the cervical sympathetic on the vessels of the rabbit's ear and the pupillary reaction, and also inhibits the vasoconstrictor fibers in the frog's sciatic nerve (Fredericque and Radelet [53]). Peripherally, caffeine also acts as a stimulant to the vagus endings (Henrijean and Honore,[54] Fredericque [50] and Barbour and Kleiner [9]).

Junkman and Stross [55] showed that the action of caffeine often parallels that of sympathetic stimulation or of epinephrine. This was found to be true in studies on the frog's pupil, blood sugar, pulse rate, large intestine, uterus and round ligament. At times, however, it acted in a directly opposite manner, as in the case of the blood vessels. Dreikurs,[56] from studies of the effects of caffeine in patients, also concluded that the autonomic changes were not always in the same direction. Using as an analogy the work of Salant and Nadler,[57] he believed that caffeine could act on either the sympathetic or the parasympathetic mechanism, depending on the predominating autonomic tone of the patient.

ORIGINAL EXPERIMENTS

In this work on caffeine, three types of experiments were undertaken. Studies were made on cats during amytal anesthesia and during ether anesthesia and on etherized animals that had been allowed to recover from the anesthesia. By use of the Forbes window technic,[58] it is possible to have a preparation that resembles the normal closed box condition of the cranium. Direct measurements of the diameter of the pial arteries were recorded from microscopic examination. Observations could also

50. Fredericque, H.: Arch. internat. de physiol. **13**:107, 1913.

51. Bardier, E.; LeClerc, P., and Stillmunkes, A.: Compt. rend. Soc. de biol. **85**:281, 1921.

52. Bardier, E.; Duchein, P., and Stillmunkes, A.: Compt. rend. Soc. de biol. **86**:4, 1922.

53. Fredericque, H., and Radelet, A.: Bull. Acad. roy. de méd. de Belgique **3**:630, 1912.

54. Henrijean, F., and Honore, D.: Mém. Acad. roy. de méd. de Belgique **20**:74, 1909.

55. Junkman, K., and Stross, W.: Arch. f. exper. Path. u. Pharmakol. **114**: 288, 1926.

56. (*a*) Dreikurs, R.: Deutsche Ztschr. f. Nervenh. **107**:184, 1928; (*b*) Wien klin. Wchnschr. **40**:156, 1927.

57. Salant, W., and Nadler, J. E.: Am. J. Physiol. **78**:308, 1926.

58. Forbes, H. S.: The Cerebral Circulation: I. Observation and Measurement of Pial Vessels, Arch. Neurol. & Psychiat. **19**:751 (May) 1928.

be made on the rate of blood flow and on the reaction of the smaller vessels. The cerebrospinal fluid pressure was read in millimeters of Ringer's solution from a straight manometer connected to a needle in the cisterna magna. Blood pressures were read from a mercury manometer connected to a cannula in the femoral artery.

In all experiments cats were used. At the onset of the experiments amytal was used for general anesthesia. The procedure was to inject 8 cc. per kilogram of body weight of a 1 per cent solution of amytal in sodium hydroxide intraperitoneally. This, as a rule, was sufficient to produce a complete and deep generalized anesthesia lasting throughout the entire experiment. With the animal under anesthesia, the operative and experimental procedures were undertaken. In an attempt to study the effect of the type of anesthesia on the action of caffeine (since Forbes and his co-workers [59] had shown that the response of cerebral vessels to histamine is dependent on the anesthesia), a series of experiments during ether anesthesia was undertaken. In this group the animals were kept under light ether, and the experiment was conducted as already described. Still another series of experiments was undertaken in an attempt to approximate the normal waking condition. In this series the animals were put under light ether anesthesia, the operative and experimental procedures were done, local procaine hydrochloride was used, and the animal securely tied in place. After the apparatus was in order, the ether was removed, and the animal was allowed to come out of anesthesia until the superficial reflexes were present. When the animal was out of anesthesia the caffeine sodio-benzoate was administered intravenously, and the results were recorded as usual.

It was also possible to introduce a solution of caffeine sodio-benzoate through the needles attached to the window. Thus the caffeine could be brought in direct contact with the pial vessel, and by this means the local effects of a solution of caffeine of a known concentration could be studied. In these experiments care was taken to disturb the relationships of the cerebrospinal fluid pressure as little as possible. A syringe containing the caffeine sodio-benzoate was introduced into the end of the needle fastened into the frame of the window (Forbes [58] 1928, fig. 1). The caffeine passed through the needle and spread out under the window. Care was taken to exert no pressure on the plunger, because this would result in a rise of cerebrospinal fluid pressure. The stopper was removed from the inferior needle, fastened to the window, and as the caffeine was introduced under the window, drops of spinal fluid would drip out through the lower needle. After a given amount was introduced the syringe was removed, the window needles were stoppered again, and readings were made. It was, of course, possible to observe

59. Forbes, H. S.; Wolff, H. G., and Cobb, S.: Am. J. Physiol. **89**:266, 1929.

the vessels in the microscopic field during the introduction of the caffeine and in this way to record the earliest change visible.

In almost all experiments, caffeine and sodio-benzoate (Lilly or Parke-Davis) was used. The solutions were made up by diluting the prepared ampule containing 7½ grains (0.49 Gm.) in 2 cc. of fluid up to 7.5 cc. with physiologic solution of sodium chloride. This solution would contain 1 grain (0.06 Gm.) per cubic centimeter, which in turn is equivalent to 32 mg. of caffeine. In a few experiments, as a control, caffeine citrate and caffeine chloride were used instead of the caffeine sodio-benzoate. The caffeine introduced under the window was at approximately body temperature. The animals were kept at room temperature and, when necessary, were kept warm by covers and a heated bulb under the operating table.

1. *Experiments During Amytal Anesthesia.*—(*a*) Effects After Intravenous Administration: This series includes twenty experiments on cats. The technic consisted in the intravenous injection of various doses of caffeine sodio-benzoate (Parke, Davis or Lilly) diluted with Ringer's solution so that 1 cc. of solution contained 1 grain of caffeine sodio-benzoate (32 mg. of caffeine). As a rule, the caffeine was injected into the femoral vein. The animals were under general anesthesia as the result of the intraperitoneal injection of 8 cc. per kilogram of body weight of a 1 per cent solution of amytal (iso-amyl-ethylbarbituric acid) kept at room temperature.

A typical experiment is presented on chart 1. A female cat, weighing 3.2 Kg., received 26 cc. of 1 per cent amytal intraperitoneally. Tracheotomy was done, the window was screwed into place, and the manometers for measuring the cerebrospinal fluid and the blood pressure were connected with needles inserted into the cisterna magna and the femoral artery. The pial artery had a diameter of 108 microns and was observed for a preliminary period of twenty minutes to get an adequate base line. During this time there was no change in the diameter of the artery, and the curve is flat. During the preliminary period the spinal fluid readings ranged between 24 and 31 mm. of Ringer's solution. The blood pressure registered at the start 123 mm. of mercury, but for the next four minutes it varied from 117 to 100 mm., with moderately large pulsations. When 2½ grains (0.16 Gm.) of caffeine sodio-benzoate was injected intravenously, the artery dilated from 108 to 115 microns during the time of injection (one-half minute). During the next half minute it dilated to 126 microns. The artery continued to dilate slowly for the next two minutes, when it reached the maximum peak of its curve, at 144 microns, three minutes after the caffeine sodio-benzoate had been injected. This represented a dilatation of 33 per cent of the initial reading. The artery retained this peak for a minute and a half and then began to constrict slowly. Ten minutes after the caffeine had been given, the arterial reading was 135 microns. Twenty minutes after caffeine, it was 126 microns, and thirty-four minutes after caffeine the reading was 121 microns, considerably lower than the peak of the curve, but dilated much beyond its original value. The artery had not yet returned to its original level at the close of the experiment, thirty-nine minutes after the caffeine.

The reading for the cerebrospinal fluid pressure during the preliminary period of this experiment varied between 24 and 31 mm. of Ringer's solution. During the injection of the caffeine it rose to 45 mm., and one-half minute later had almost attained its maximum at 59 mm. During the next half minute it reached its maximum of 61 mm., which it retained for about one minute. The spinal

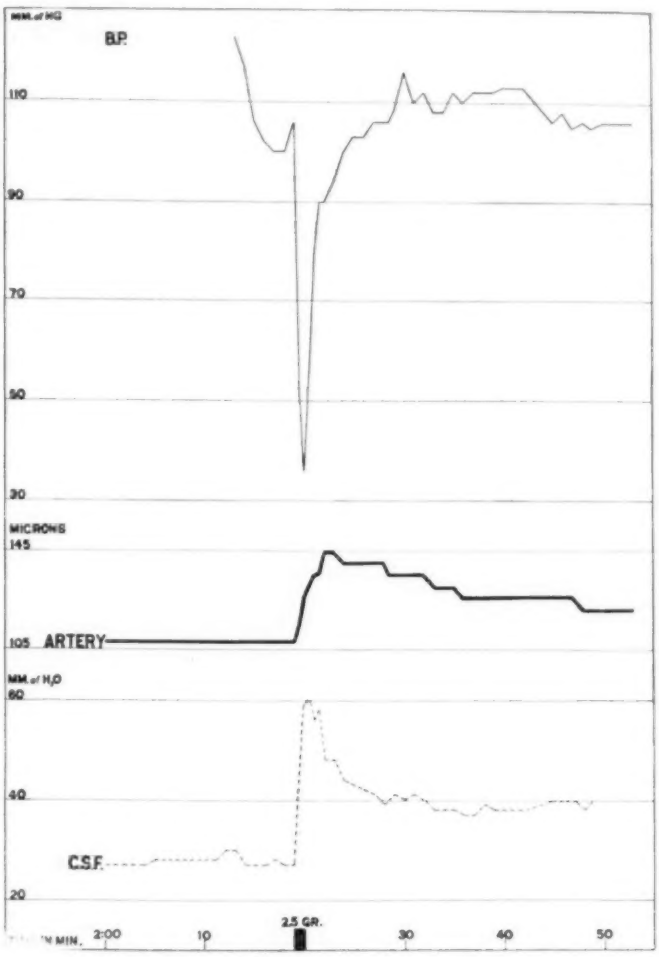

Chart 1.—Caffeine sodio-benzoate; amytal anesthesia. Dilator effect of 2½ grains of caffeine sodio-benzoate intravenously (23.5 mg. per kilogram) on a pial artery accompanied by a fall in systemic blood pressure (*B. P.*) and a rise in cerebrospinal fluid pressure (*C. S. F.*) during amytal anesthesia.

fluid pressure then dropped rather rapidly to 44 mm., which was the reading five minutes after the caffeine had been given. After this the spinal fluid pressure continued to fall slowly for the next five minutes, reading 40 mm. ten minutes after the caffeine had been given. The spinal fluid pressure remained at about this level

until the end of the experiment, thirty minutes after the caffeine had been injected. The rise in spinal fluid pressure at the peak of its curve was 35 per cent of the initial pressure.

The blood pressure curve is also of interest. Five minutes before the caffeine was introduced, the blood pressure curve was between 123 and 100 mm. of mercury. During the injection of the caffeine the blood pressure dropped decisively from 106 to 54 mm., the next half minute being 56 mm., and the next reading after a half minute was 80 mm. Five minutes after the caffeine had been given, the blood pressure was back to 100 mm., and ten minutes after the caffeine it was 108 mm. of mercury. The blood pressure was at a fairly constant level, from 108 to 116 mm., for the remaining twenty minutes of the experiment. The picture was that of an acute drop lasting from two to three minutes, followed by a return to the normal level.

There were other changes due to the administration of caffeine. First, when the artery was dilating the pia became redder, and one could notice that the other arteries and even arterioles, as small as were measurable by our technic (from 9 to 10 microns), were dilating. The same was true, but not so consistently, of the small veins and venules. In the smaller arteries and in the veins, where the blood flow of the red cells is visible within the vessel, the velocity increased. The color of the vessel field was redder than before, this being due probably to the dilatation of the vessels and the increased velocity of the blood.

Chart 2 shows the response to smaller doses of caffeine sodio-benzoate. A male cat weighing 3.7 Kg. received 28 cc. of 1 per cent amytal intraperitoneally and 4 cc. intravenously. At the beginning of the experiment the diameter of the pial artery was 198 microns; the blood pressure taken from the femoral artery was 96 mm., and the cerebrospinal fluid pressure was 76 mm. Observations of the artery were made for a preliminary period of ten minutes, and then the animal was given 1 grain (7.8 mg. per kilogram) of caffeine sodio-benzoate (Parke, Davis solution) intravenously in one-half minute. During the time of the injection the artery dilated from 198 to 225 microns. It continued to dilate for the next quarter of a minute until it had reached a level of 234 microns, a dilatation of 18 per cent over its initial value. The next quarter of a minute it had passed its peak, and the reading was 225 microns. The artery continued to contract slowly until it had returned to its initial size of 198 microns within six minutes after the caffeine sodio-benzoate had been given. The spinal fluid pressure during the preliminary period of ten minutes was at a level of from 76 to 77 mm. of Ringer's solution. On the administration of caffeine, there was a sudden rise to 86 mm. during the time of injection. This was the peak and represents a small dilatation of 13 per cent of its initial value. During the next three and a half minutes it slowly fell, until it reached a level of 73 mm.; at the same time the artery had returned to its original value. Two minutes after this (nine minutes after the administration of the caffeine), it had reached a value of 72 mm., the lowest during the experiment. The blood pressure during the preliminary period was about 74 mm. of mercury. On the administration of the caffeine, it dropped from 74 to 54 mm. during the injection time. During the next quarter of a minute it had reached 50 mm., its lowest value, which represents a drop of 34 per cent. During the next minute it had gone up to a level of 76 mm., where it remained fairly constant. The blood pressure had recovered its initial value within three minutes after the caffeine had been injected.

During the injection time and for the following few minutes, other changes could be seen. Pulsation of the pial arteries was noted. There was a general

dilatation of all the vessels visible, and there was an increase in blood flow. The respiratory rate increased, and this increase persisted for about ten minutes after the administration of caffeine.

The experiment was repeated with a larger dose of caffeine sodio-benzoate. After a reasonable preliminary period, during which the artery was 198 microns, the cerebrospinal fluid pressure from 81 to 83 mm. of Ringer's solution, and the blood pressure 74 mm. of mercury, the animal was given 1½ grains (0.09 Gm.) (13.2 mg. per kilogram) intravenously. The response was the same as before, only somewhat greater. The artery dilated from 198 to 261 microns during the forty-five seconds allowed for injection. This was a change of 12

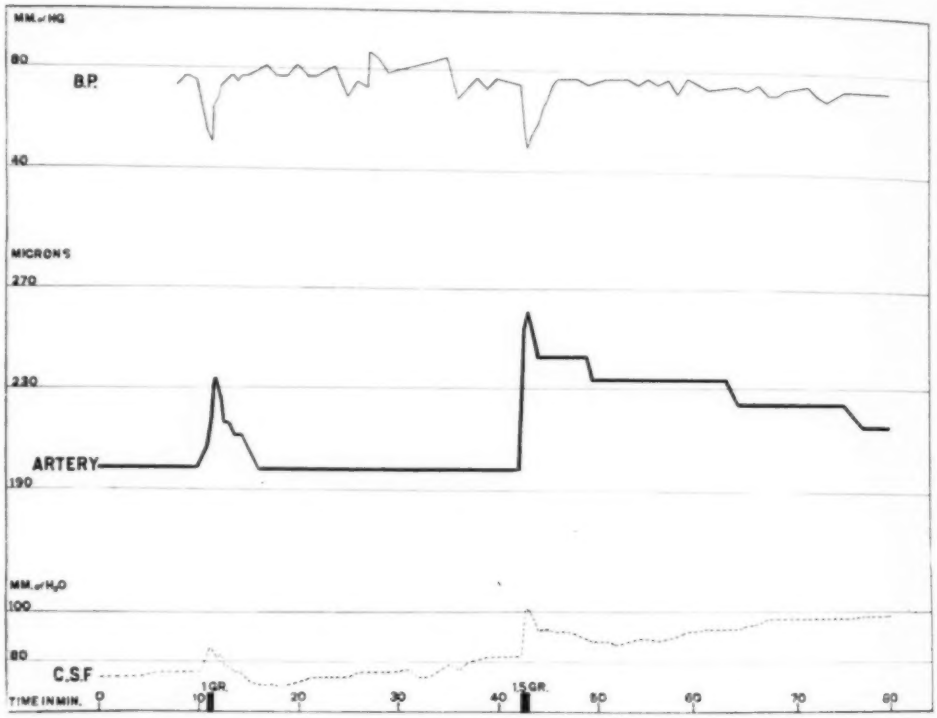

Chart 2.—Caffeine sodio-benzoate. Dilator effect of two small doses of caffeine sodio-benzoate intravenously (7.8 and 13.2 mg. per kilogram) on a pial artery, accompanied by a fall in systemic blood pressure (*B.P.*) and a rise in cerebrospinal fluid pressure (*C.F.S.*) during amytal anesthesia. The second dose was not given until the artery, blood pressure and cerebrospinal fluid pressure had returned to the preliminary values.

per cent over its initial value. It remained at 261 microns for half a minute, and then, within the next minute, dropped to 243 microns. From this point the constriction took place slowly, and at the end of the experiment, forty minutes after the administration of caffeine, the diameter of the artery was 216 microns. It was not for an hour and thirteen minutes after the caffeine had been given that the artery returned to its preliminary level. The spinal fluid pressure before the use of caffeine was from 81 to 83 mm. of Ringer's solution.

During the injection period it rose to a value of 101 mm. and in the next minute dropped back to from 93 to 94 mm. It slowly fell for three minutes, until it reached a level of from 89 to 90 mm. Twenty minutes after the caffeine had been given, it rose slightly and was at about the level of 100 mm. at the end of the experiment. The second slow rise is probably not the result of the caffeine,

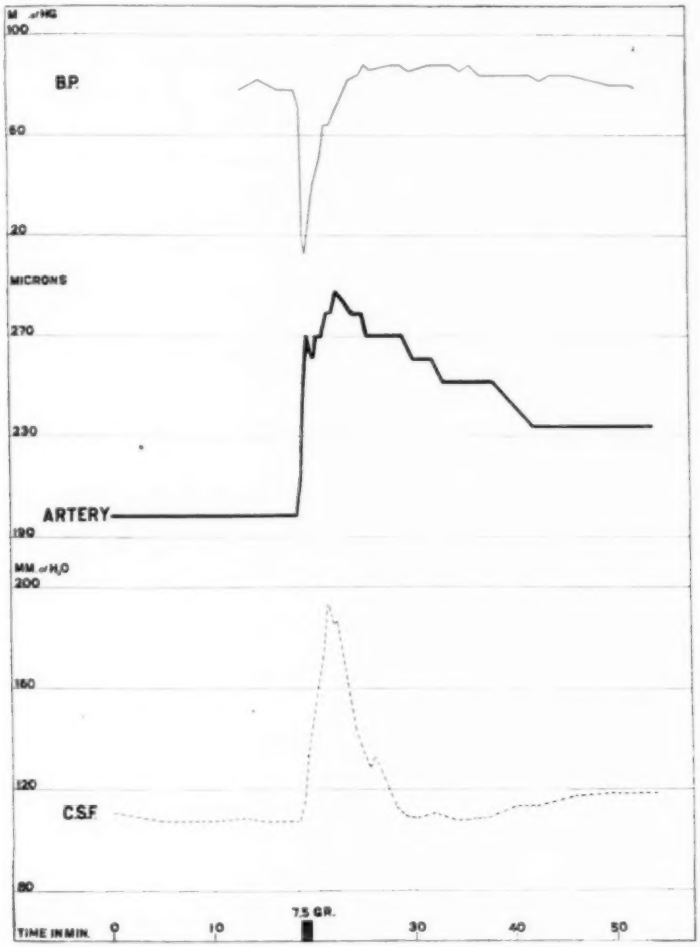

Chart 3.—Caffeine sodio-benzoate. Dilator effect of a very large dose of caffeine (7½ grains intravenously, 63 mg. per kilogram) upon a pial artery, accompanied by a fall in systemic blood pressure (*B.P.*) and a rise in cerebrospinal fluid pressure (*C.S.F.*) during amytal anesthesia.

but of general cerebral edema, as has often been observed in long experiments. The blood pressure in this experiment dropped rather suddenly from 74 mm. to a level of 48 mm. during the injection period. It then slowly rose within the next two and a half minutes to its initial value and remained there until the end of the experiment.

Chart 3 shows the effect of a larger dose, 7½ grains (63 mg. per kilogram), of caffeine sodio-benzoate on the same animal. In this experiment the artery was constant at 198 microns; the cerebrospinal fluid pressure was at from 107 to 108 mm. of Ringer's solution, and the blood pressure was at from 78 to 82 mm. of mercury during the preliminary period. The animal received 7½ grains of caffeine sodio-benzoate (Parke, Davis solution) in 2 cc. in 30 seconds. The artery dilated to 216 microns during the injection and rose to 270 microns within a minute after the injection. It constricted to 261 microns for a minute, and then dilated to 288 microns, its peak being four minutes after the administration of caffeine. The dilatation was 45 per cent. After this it slowly constricted until thirty minutes after the caffeine had been given, when the experiment was ended; it then had reached a level of 234 microns. The spinal fluid pressure rose

TABLE 1.—*Effect After Intravenous Administration of Caffeine Sodio-Benzoate During Amytal Anesthesia*

	Dose		Diameter of Artery, Microns			Blood Pressure, Mm. of Mercury			Cerebrospinal Fluid Pressure, Mm. of Ringer's Solution		
Experiment	Caffeine Sodio-Benzoate, Grains	Caffeine, Mg. per Kilogram	Before	After	Per Cent	Before	After	Per Cent	Before	After	Per Cent
I	3/10	2.5	171	171	0	...	...	....	41.5	41.5	0
II	3/10	2.7	252	252	0	...	...	....	35.5	33.5	+ 6
III	3/10	2.7	252	270	+ 7	...	...	....	33.5	78.0	+13
IV	½	4.5	252	288	+14	90	70 to 92	−22	27.0	37.0	+37
V	5/8	5.5	171	225	+31	...	...	....	39.5	42.0	+ 6
VI	¾	7.0	198	234	+18	...	...	....	82.0	79.0	− 4
VII	1	7.8	198	216	+18	141	135 to 153	−12	11.0	13.5	+22
VIII	1	8.6	153	198	+29	50	35	−30	15.0	15.0	0
IX	1	9.0	270	306	+13	68	54 to 61	−20	45.0	51.0	+13
X	1⅛	10.0	180	234	+33	...	...	....	83.0	98.5	+19
XI	1½	13.2	198	261	+32	94	68 to 94	−28	83.0	100.0	+20
XII	2	16.0	234	360	+59	102	60	−41	16.0	50.0	+212
XIII	2	18.0	252	306	+21	45	32 to 69	−29	41.0	81.0	+97
XIV	1	18.0	207	234	+18	94	70	−26	77.0	86.0	+12
XV	2½	24.6	261	333	+28	105	74	−39	95.0	133.0	+40
XVI	2⅛	25.3	108	144	+33	106	36	−66	29.0	61.0	+11
XVII	2½	26.1	198	306	+45	99	68 to 99	−31	35.0	85.0	+143
XVIII	2½	27.0	153	207	+35	...	...	....	25.0	29.0	+16
XIX	3	32.5	153	225	+47	116	65	−44	22.0	31.0	+49
XX	7½	63.0	198	288	+45	78	12 to 70	−846	108.0	193.0	+79

from a level of from 107 to 108 to 115 mm. during the injection period. Two and a half minutes after the caffeine had been given, it had reached a level of 293 mm., an increase of 17 per cent over its initial value. The blood pressure took a sudden drop from 78 to 82 to 12 mm. of mercury within forty seconds after the injection was started. Within two minutes it was back at a level of 42 mm., and continued to rise until it had attained its preliminary level within six minutes after the administration of caffeine. It remained at this level until the end of the experiment. In this experiment as well there was noted a generalized dilatation of the smaller vessels; the color was redder, and the velocity was greater.

In table 1 are presented the results of experiments on the effects of the intravenous injection of caffeine. Caffeine citrate was used in experiment 14, and caffeine chloride in experiment 15. In all the others caffeine sodio-benzoate was used (Parke, Davis solution in experiments 1 to 10, 13 and 18, and Eli Lilly solution in the rest). Since the

response in all these experiments was in the same direction, we feel justified in believing that the caffeine was the effective agent. Various quantities were injected as tabulated, the smallest dose giving a measurable change in the artery being 2.7 mg. per kilogram. Smaller doses were tried, but gave no response. The largest dose used was 63 mg. per kilogram. In general, larger doses gave a greater response than smaller doses, but this did not seem to hold absolutely. The explanation of this probably lies in the fact that the response depends on the initial size of the artery, which in turn depends on the degree of anesthesia in these animals.

In all of the experiments in which caffeine caused a change (eighteen of twenty) of the pial artery, it caused dilatation. This dilatation varied from 7 to 53 per cent. In seventeen of the twenty experiments there was an increase in cerebrospinal fluid pressure; in two experiments there was no change, and in one a drop of 4 per cent. Measurements of the blood pressure were made in thirteen, and in all cases there was a sudden drop in blood pressure immediately on intravenous injection, which was followed by a return within three or four minutes generally to the initial level, in three cases to a level slightly above the initial one. It is of importance to note that in all of these experiments the initial blood pressure level was well within normal limits. In all of these experiments the vagus and sympathetic nerve trunks were intact.

In some of the experiments artificial respiration was used in an attempt to rule out changes in the arterial diameter due to respiratory changes as the result of using caffeine. This was done by having a rhythmic interrupter between a source of compressed air and the tube connected to the tracheal cannula. In the experiments under artificial respiration the response to caffeine was found to be exactly the same as that in the other experiments, the artery, cerebrospinal fluid and blood pressure reacting exactly as in the experiments in which artificial respiration was not used. It was often noted, as in experiments 15 and 16, that the dilatation of the artery took place before the change in respiration was noted. From other experiments it was thought that the dilatation followed too soon after the administration of the drug to be attributed to a change in respiration. Then in some cases the artery had already constricted and was back again to its normal level, while the respiration was still noted to be rapid.

These considerations suggested that in these experiments the change in respiration due to the caffeine did not affect the results. It is also of interest that in these experiments the rise in cerebrospinal fluid seemed almost simultaneous with the dilatation of the artery. (Our observations, however, were not frequent enough to settle this point absolutely.) As a rule, the spinal fluid pressure rose as the artery

dilated. This was observed repeatedly. The smallest artery measured by this technic was 9 microns in diameter. These observations show that when the larger artery dilated there was a similar dilatation of all the smaller arteries and arterioles down to the size measurable by this technic. No quantitative evidence of changes in the diameter of the very small arterioles, venules and capillaries is presented. It was observed repeatedly, however, that on the intravenous administration of caffeine during amytal anesthesia the entire microscopic field became redder. This change in color was presumably due to the dilatation of the arterioles, venules and capillaries. These vessels reacted exactly as did the measurable arteries. In two experiments, moderately large veins were measured and reacted in the same direction as the artery but not to such a marked degree. At the same time that the dilatation was noted, there was also a marked speeding up of the circulation. The artery looked redder, and in the smaller arterioles, venules and veins, where the flow is normally visible, there was a definite increase in velocity of the red cells. The fact that the velocity of the blood flow increases in the arterioles, as well as in the venules and veins, shows that there must also be an increase in velocity of the blood through the capillaries.

(*b*) Effects After Local Administration: Experiments were carried out to test the local effect of caffeine when brought into direct contact with the cerebral vessels. In these experiments, caffeine sodio-benzoate was diluted with Ringer's solution to the desired concentration. The solution was brought to approximately the body temperature of the animal and introduced under the window. The exact procedure has already been described.

A typical experiment is as follows: A male cat, weighing 5.2 Kg., was given 4.2 cc. of sodium amytal (Eli Lilly ampules) intraperitoneally before the operative procedure. The anesthesia seemed light during the experiment, and an additional 5 cc. of sodium amytal was given intraperitoneally. During the preliminary period of ten minutes, the arterial diameter was 189 microns constantly. The cerebrospinal fluid pressure averaged about 41 mm. of Ringer's solution. The blood pressure for four minutes preceding the administration of caffeine sodio-benzoate averaged about 96 mm. of mercury. The caffeine solution was diluted with Ringer's solution as indicated so that 1 cc. contained 1 grain of caffeine sodio-benzoate (32 mg. of caffeine). When the cork stopper was removed from the needle in the window frame, the spinal fluid pressure dropped from 41 to 37 mm. due to a sudden release of pressure. The tip of the syringe was inserted into the upper needle, the stopper was removed from the lower needle, and the caffeine solution slowly flowed through the needle under the window. One and a half cubic centimeters of caffeine was allowed to flow in before the lower needle opening was stoppered, the syringe removed and the upper needle hole stoppered. Ten seconds after the caffeine had started to flow, the pial artery immediately dilated from 189 to 216 microns; the spinal fluid pressure rose to its preliminary level of 41 mm. The blood pressure dropped slightly to 94 mm. Thirty seconds after the caffeine had been given, the diameter of the artery was 225

microns, and forty seconds after the caffeine, the diameter was 234 microns. The pia looked considerably redder, there was a generalized dilatation of all visible vessels, and the blood flow seemed more rapid. During the next half minute, the artery dilated, reaching its maximum value of 297 microns one minute and fifteen seconds after the caffeine had been given, a change of 62 per cent over the preliminary reading. At this point the specified amount of solution had been introduced, and the syringe was removed. The artery maintained this maximum level for half a minute and then constricted down to a level of 290 microns, and two and a half minutes after the caffeine reached the pial vessels the diameter was 252 microns. From this point the vessel gradually became narrower and reached its maximum level in about nine minutes. As the artery became narrower the entire field became paler, obviously due to constriction of the other vessels in the microscopic field. The spinal fluid pressure remained fairly constant and at the preliminary level. No change was reflected from the arterial dilatation or from the manipulation. There was also little change in the blood pressure level, showing that the change in the pial vessel was purely a local change and was reflected neither in the blood pressure nor in the cerebrospinal fluid readings. This has been the common picture on the local introduction of caffeine sodio-benzoate under the window.

As a control, the same amount of Ringer's solution at about the animal's temperature was introduced. In this particular experiment the artery dilated from 189 to 198 microns; the spinal fluid remained the same. The blood pressure was not taken. This dilatation lasted three minutes; then the diameter was 189 microns. This result is not the usual one, but is presented because it is part of the same experiment. There was no observable change in the smaller vessels. After the artery had been at its preliminary level for six minutes, the same experiment was repeated, caffeine sodio-benzoate being used, and the result this time was exactly the same as that already reported. The artery dilated from 189 to 288 microns, a change of 52 per cent over its preliminary value. This vessel was pulsating during the administration of caffeine, and the small vessels were dilated and looked redder exactly as already described. After the artery had reached its peak, it slowly returned to normal within the course of the next seven and a half minutes. The spinal fluid pressure did not change its level and was fairly constant at its preliminary value until the experiment was over.

The series of experiments after local administration is presented in table 2. It is obvious that in all cases there was a dilatation of the pial vessel ranging from 11 to 57 per cent. In three experiments there was a rise in blood pressure of from 5 to 8 per cent. In the others there was no change in blood pressure. The cerebrospinal fluid pressure was followed in eight experiments, and of the two shown there was a slight rise of from 2 to 6 per cent. The others showed no change whatever. The control experiments as a rule showed little if any change in the artery, spinal fluid or blood pressure. In addition to this control series there is much evidence showing that the mere introduction of small quantities of Ringer's solution does not produce changes in any of these three factors. The local effect was not limited to the vessel that happened to be selected for measurement. All the visible vessels responded

in exactly the same way. There were no actual measurements, however, on the vessels smaller than 9 microns, owing to the limitation of the technic.

2. *Experiments During Ether Anesthesia.*—(*a*) Effects After Intravenous Administration: The second group of experiments tested the effect of caffeine sodio-benzoate on the cerebral circulation in cats during ether anesthesia. The animals were given ether by means of an ether cone until they were under anesthesia. At this point, when the animal was completely relaxed and all reflexes had disappeared, a tracheotomy was done and a glass cannula tied into the cut trachea. During the earlier experiments the animal was kept in anesthesia by keeping cotton soaked in ether directly in front of the glass cannula.

TABLE 2.—*Effect After Local Administration of Caffeine Sodio-Benzoate During Amytal Anesthesia*

Experiment	Dose: Caffeine Sodio-Benzoate, Grains	Dose: Caffeine, Mg. per Kilogram	Diameter of Artery, Microns: Before	Diameter of Artery, Microns: After	Diameter of Artery, Microns: Per Cent	Blood Pressure, Mm. of Mercury: Before	Blood Pressure, Mm. of Mercury: After	Blood Pressure, Mm. of Mercury: Per Cent	Cerebrospinal Fluid Pressure, Mm. of Ringer's Solution: Before	Cerebrospinal Fluid Pressure, Mm. of Ringer's Solution: After	Cerebrospinal Fluid Pressure, Mm. of Ringer's Solution: Per Cent
I	5/10	2.5	252	270	+11	72	76	+5	..	..	....
II	2	17.0	504	594	+19	48	48	0	34	34	0
III	1½	18.0	189	297	+57	80	80	0	30	30	0
IV	1½	18.0	189	288	+52	82	82	0	..	..	....
V	3/5	4.5	243	270	+11	52	56	+7	89	89	0
VI	1⅕	9.0	270	306	+13	80	80	0	92	92	0
VII	1⅘	13.5	261	324	+28	100	100	0	50	50	0
VIII	2⅘	18.0	90	117	+30	72	78	+8	55	55	0
IX	1½	20.0	180	234	+23	40	40	0	82	84	+2
X	3	35.0	180	243	+35	48	48	0	98	104	+6

In the later experiments use was made of an ether bottle, and in two experiments an attempt was made to regulate the supply of ether given the cat by attaching the apparatus for artificial respiration to the ether bottle, thus sending a constant stream of air mixed with ether through the tracheotomy tube. Later it was found that the anesthesia was more uniform if the ether bottle was merely connected by a rubber tube to the tracheal cannula, allowing the spontaneous breathing of the animal to regulate the amount of ether required. After the anesthesia had been adjusted, the operative procedure was carried out as already described in section 1.

The operative procedure caused considerably more bleeding during ether anesthesia than during amytal anesthesia. Undoubtedly this was due to the general vasodilatation throughout the skin, muscle, bone and meninges. It was also necessary to be more careful in reducing the spinal fluid pressure before the window could be screwed into place, for ether increases the spinal fluid pressure. This has a tendency to cause the brain to herniate through the trephine hole, and to touch the under-

surface of the window while it is being screwed into place. As soon as the apparatus was adjusted, it was important again to regulate the supply of ether so that the animal was getting a constant mixture. Any variation in the ether ratio was reflected in changes of the diameter of the artery. A richer ether mixture tended to increase the diameter of the artery, while a leaner mixture resulted in a constriction.

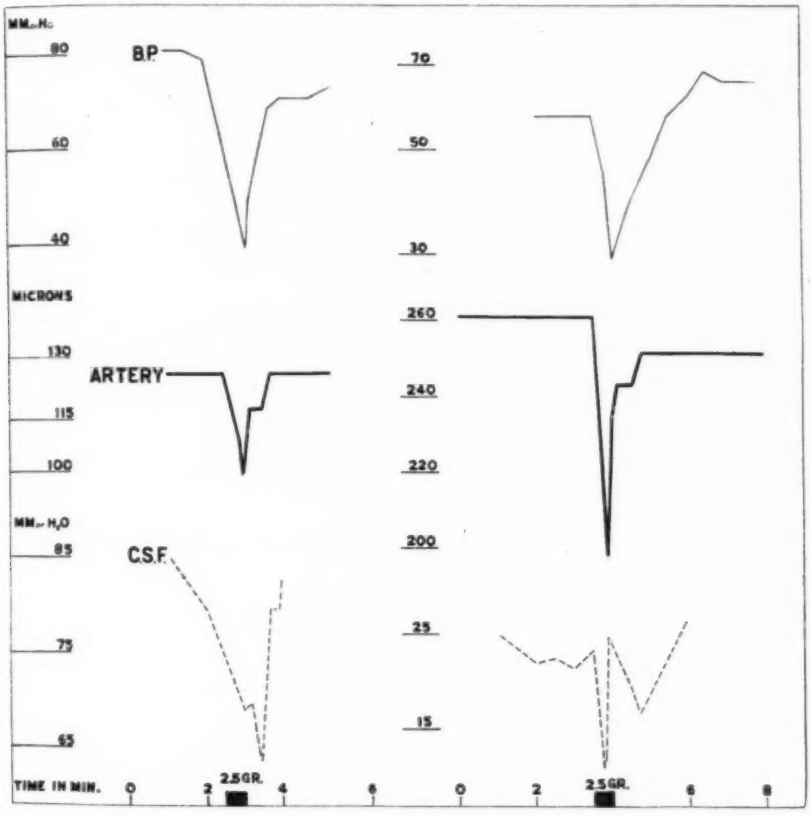

Chart 4.—Caffeine sodio-benzoate with ether. Two experiments illustrating the constrictor effect of caffeine (22.5 and 27 mg. per kilogram) administered intravenously on the diameter of the pial arteries accompanied by a fall in systemic blood pressure (*B.P.*) and a fall in cerebrospinal fluid pressure (*C.S.F.*) during ether anesthesia.

The pial vessels in these experiments looked much redder at the onset than they had in the experiments with amytal. This was undoubtedly due to the generalized vasodilatation resulting from the ether.

A typical experiment is presented in chart 4. A male cat, weighing 3.4 Kg., was given ether at 9:30 a. m. As soon as the animal was under anesthesia,

the tracheal cannula was tied in place, and the anesthesia was continued by means of holding cotton soaked with ether in front of the cannula. The operation was completed about 10:30. At this time the diameter of the artery was 261 microns, the spinal fluid reading 49 mm. of Ringer's solution, and the blood pressure 79 mm. of mercury. The artery varied from 270 to 252 microns, depending on the amount of ether. Finally, the mixture was regulated so that the artery remained constant at 261 microns throughout the ten minute preliminary period. During this preliminary period the cerebrospinal fluid pressure was about from 24 to 25 mm., and the blood pressure was 59 mm. When a satisfactory base line had been obtained, the animal was given 2½ grains of caffeine sodio-benzoate intravenously in twenty seconds. Immediately, there was an acute vasoconstriction of the artery, the diameter decreasing from 261 to 216 microns during the injection period. Five seconds later, the diameter of the artery was 198 microns; this was the lowest reading during the experi-

TABLE 3.—*Effect After Intravenous Injection of Caffeine Sodio-Benzoate During Ether Anesthesia*

Experiment	Dose: Caffeine Sodio-Benzoate, Grains	Dose: Caffeine, Mg. per Kilogram	Diameter of Artery, Microns: Before	After	Per Cent	Blood Pressure, Mm. of Mercury: Before	After	Per Cent	Cerebrospinal Fluid Pressure, Mm. of Ringer's Solution: Before	After	Per Cent
I	3½	17.0	162	135	—11	93 to 119	32.0	—66	49.5	22.0	—56
II	2½	20.0	234	207	—12	79.0	31.0	—60	55.5	21.0	—62
III	2½	22.5	126	99	—21	79.0	37.0	—53	79.5	63.5	—20
IV	2	23.0	144	99	—31	78.0	54.0	—31	51.5	49.5	— 4
V	2½	24.0	262	207	—21	90.0	38.0	—48	51.5	49.5	— 6
VI	2½	27.0	261	198	—24	59.0	29.0	—51	21.5	11.0	—49
VII	2½	25.0	288	225	—30	62.0	22.0	—65	15.5	14.5	—65
VIII	2½	27.0	262	207	—21	98.0	78.0	—20	34.5	28.5	—17
IX	2½	30.0	198	180	— 9	....	....	....	97.5	73.0	—25
X	2½	30.0	198	189	— 5	....	....	....	10.3	89.0	—14

ment, representing a decrease of 25 per cent from the preliminary level. Ten seconds later, the artery had begun to dilate again, and seventy-five seconds after the start of the injection of caffeine the artery had dilated to a diameter of 243 microns. It remained at this level for half a minute and then dilated to 252 microns. It remained at this level for five minutes and did not reach its preliminary value until seven minutes after the caffeine had been introduced. Immediately on the injection of the caffeine, the spinal fluid took a sudden drop from 21.5 to 11 mm. of Ringer's solution B, a decrease of 48 per cent from its base line level. Then it began to rise (more slowly than the dilatation of the artery) and was back at its preliminary level in two and a half minutes. The blood pressure curve dropped from 59 to 29 mm. of mercury, a drop of 50 per cent. It then immediately began to rise, and within two minutes had returned to its original level. This was sustained until the close of the experiment. During the time when the blood pressure took this sudden drop, the flow was seen to become slower for an instant, and the artery looked blue. With the return of the blood pressure to its original level, the artery once more looked bright red as during the preliminary period.

The series of experiments during ether anesthesia is shown in table 3. In all but one of these experiments the caffeine was introduced intravenously. In experiment 9 it was introduced subcutaneously.

The dosage in these cases varied from 17 to 30 mg. per kilogram. In all cases there was a vasoconstriction, the diameter of the blood vessel varying by from 4.5 to 21.9 per cent. Even in experiment 9 there was a vasoconstriction of 9 per cent. There does not seem to be any quantitative correlation between the amount of change and the size of the dose given. In all probability the depth of anesthesia varied, and the reactivity of the artery to caffeine is undoubtedly dependent on the depth of anesthesia. In all these experiments there was a definite drop in cerebrospinal fluid pressure, from 4 to 55 per cent, directly associated with the vasoconstriction. This was also present in experiment 9. In the experiments during which measurements of the blood pressure were made there was a marked fall in each case. This drop was sudden and lasted, as a rule, for a few minutes and then returned to its initial value or thereabouts. These results were constant and uniform throughout all of the experiments.

(*b*) Effects After Local Administration: A series of experiments was undertaken to show the local effect of caffeine sodio-benzoate during ether anesthesia. The procedure was exactly that described under section 1 (*b*). Adequate controls of Ringer's solution were used in all cases. A typical experiment will be described.

A male cat, weighing 3.4 Kg., was anesthetized with ether. When the experimental set-up was in order the diameter of the artery was 261 microns, the blood pressure was 27 mm. of mercury and the spinal fluid was 24 mm. of Ringer's solution. These remained constant for a five minute preliminary period. After this period the upper cork stopper of the window was removed, the syringe containing the caffeine sodio-benzoate warmed to approximately body temperature was put in place, the lower cork stopper was removed, and 1 cc. of solution containing 14 mg. of caffeine per kilogram of body weight was introduced under the window. After the quantity of caffeine had been allowed to flow under the window, the lower cork stopper was replaced, the syringe removed and then the upper stopper replaced. During the entire manipulation the artery remained perfectly constant at 261 microns, and there was no change in the blood pressure. The spinal fluid pressure rose slightly from 24 to 28 mm. of Ringer's solution on the introduction of the caffeine. It remained at this level until the syringe was out and the cork stopper replaced. Then it dropped to 26 mm. of Ringer's solution, which level it retained. This change was undoubtedly due to the slight increase in spinal fluid pressure resulting from the pressure applied to the syringe.

The results of the local application of caffeine under the window are presented in table 4. In all cases but one (experiment 4) there was no change in the diameter of the artery. In experiment 4 the size of the artery became smaller, probably as the result of the mechanical pressure resulting from the local introduction. This lasted only so long as the syringe was in place. After the syringe was removed the artery returned to its preliminary level and remained there without further change.

In seven cases when the blood pressure was taken there was no change recorded. In all cases spinal fluid readings were taken in millimeters of Ringer's solution, and in all but one (experiment 5) there was no change in spinal fluid pressure. In experiment 3 the spinal fluid pressure rose immediately while the caffeine was being introduced, reaching its maximum reading of 28 mm. during the injection and then fell to a level of 24 mm., where it remained throughout the rest of the experiment. This change, occurring coincidently with the introduction of caffeine, is undoubtedly the result of the mechanical pressure from the syringe required to introduce the solution under the window. The results of this series of experiments indicate in general that caffeine sodio-benzoate had no direct, local effect on the pial artery when introduced under the window. The blood pressure and spinal fluid pressure were also unchanged. It is important to note that ether dilates the pial artery, so that in this series of experiments the caffeine was acting on a dilated artery.

TABLE 4.—*Effect After Local Administration of Caffeine Sodio-Benzoate During Ether Anesthesia*

Experiment	Dose: Caffeine Sodio-Benzoate, Grains	Dose: Caffeine, Mg. per Kilogram	Diameter of Artery, Microns: Before	Diameter of Artery, Microns: After	Diameter of Artery, Microns: Per Cent	Blood Pressure, Mm. of Mercury: Before	Blood Pressure, Mm. of Mercury: After	Blood Pressure, Mm. of Mercury: Per Cent	Cerebrospinal Fluid Pressure, Mm. of Ringer's Solution: Before	Cerebrospinal Fluid Pressure, Mm. of Ringer's Solution: After	Cerebrospinal Fluid Pressure, Mm. of Ringer's Solution: Per Cent
I	1½	10	279	279	0	81	81	0	20.0	30.0	+50
II	1½	11	288	288	0	..	..	..	24.5	24.5	0
III	1½	14	261	261	0	40	40	0	24.5	28.5	+13
IV	1½	14	261	252	−3	40	40	0	24.5	24.5	0
V	1½	18	171	171	0	73	73	0	32.0	32.0	0
VI	1½	18	189	189	0	73	73	0	55.0	55.0	0
VII	1½	20	297	297	0	65	65	0	21.0	21.0	0
VIII	1½	20	297	297	0	78	78	0	37.0	37.0	0
IX	2	25	117	117	0	..	..	..	63.0	63.0	0
X	2	25	106	106	0	..	..	..	130.0	130.0	0

3. Experiments After Recovery from Ether Anesthesia.—(*a*) Effects After Intravenous Administration: The experiments already reported were done during the general anesthesia of amytal or ether. It is obvious that the results must be conditioned by the anesthesia used. In an attempt to approximate the normal physiologic condition, the procedure was modified. The animals were operated on under light ether anesthesia; readings were taken of the diameter of the artery, the spinal fluid pressure and the blood pressure, exactly as in the preceding experiments. Procaine hydrochloride was infiltrated into all the wounds and into every part of the animal that was in contact with the apparatus. The ether was then removed, and the animal was permitted to come out of anesthesia until the superficial reflexes were present. Readings were then taken of the diameter of the artery and the spinal

fluid and blood pressure. These were repeated until a satisfactory base line was obtained. Then caffeine sodio-benzoate was introduced intravenously or locally under the window, and the results were recorded.

The removal of the ether always caused a constriction of the artery measured and a change in the whole field. All the visible vessels became narrower, and the pia became considerably paler. As a rule, the spinal fluid pressure dropped, as did the blood pressure. In these experiments it was necessary to obtain a base line that remained constant to be sure that any change occurring in the course of the experiment was due to the effect of the caffeine and not to the removal of ether.

An experiment in this series is presented in chart 5. At the onset of the experiment the artery was 171 microns in diameter, the spinal fluid pressure was 20 mm. of Ringer's solution, and the blood pressure reading was 94 mm. of mercury. Two and a half grains of caffeine sodio-benzoate was injected intravenously in fifteen seconds. Within fifteen seconds after the injection the artery constricted to 162 microns and in twenty-five seconds after the administration of caffeine had reached a level of 144 microns, a decrease of 20 per cent below the initial reading. The artery immediately began to dilate, and within forty seconds of its lowest reading had reached a level of 171 microns. This was retained for fifty seconds, and then the artery dilated further until within thirty seconds it had reached a level of 180 microns. It persisted at this level until the end of the experiment, an increase of about 4 per cent of the preliminary value.

The spinal fluid pressure during the preliminary period was about 20 mm. of Ringer's solution. On the administration of the caffeine it rose slightly to 22 mm., remained there for twenty seconds, dropped back to 20 mm. during the next thirty seconds and then rose to 30 mm. of Ringer's solution. It retained this peak for a moment and then dropped back immediately to a level of 20 mm. During the rest of the experiment it rose again to 23 mm. and then returned to about its preliminary level. The peak of its curve showed an increase of 46 per cent over its preliminary value. The preliminary value of the blood pressure was 94 mm. of mercury. On the introduction of the caffeine, the blood pressure dropped, reaching its lowest reading, 40 mm. of mercury, twenty-five seconds after the introduction of the caffeine. It retained this low value for two minutes and then rose slightly to a value of 70 mm., which it retained until the end of the experiment. The lowest value for blood pressure represented a drop of 51 per cent of its preliminary value.

Another experiment is shown in chart 5. In this experiment the base line reading of the artery was 225 microns, the spinal fluid pressure reading was 37 mm. of Ringer's solution and the blood pressure was 94 mm. of mercury. During the administration of 24 mg. per kilogram of caffeine sodio-benzoate intravenously in twenty seconds, the artery constricted to 216 microns. Within ten seconds more it had reached a value of 207 microns and immediately began to dilate again. One minute after the caffeine had been introduced, the artery had dilated to 243 microns, at which level it remained until the end of the experiment. In this case the lowest point of the curve represents a dilatation of 16 per cent. The spinal fluid pressure dropped to 33 mm., a slight drop of 10 per cent, and within forty seconds had risen to 39 mm., slightly above its preliminary value. In thirty seconds it dropped back to its preliminary reading

of 37 mm. of Ringer's solution, which it retained until the end of the experiment. The change in the cerebrospinal fluid pressure was slight. The blood pressure level was 94 mm. On the administration of the caffeine it rose suddenly to a peak of 150 mm.; it immediately dropped to a value of 58 mm. and within forty seconds after the introduction of the caffeine had reached a value of 50 mm; it rose slightly and remained at 58 mm. of mercury until the end of the experiment. At its peak it represented an increase of 57 per cent, and at its lowest level a change of 46 per cent.

It is of interest that in this experiment there was an acute rise in blood pressure followed by a fall after the intravenous introduction of caffeine. In

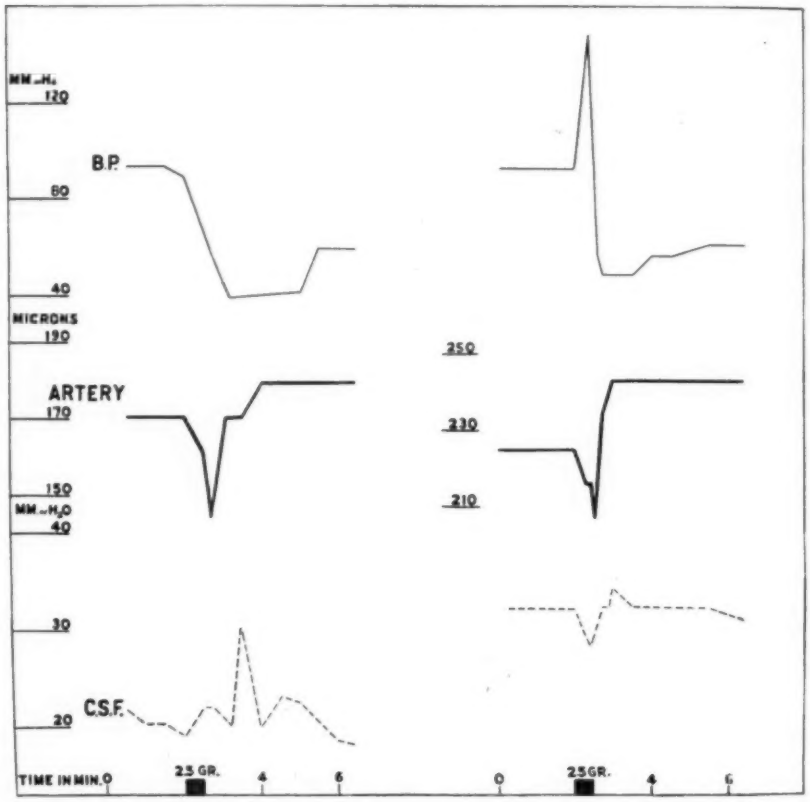

Chart 5.—Caffeine sodio-benzoate without ether. Two experiments illustrating the effect of caffeine (24 and 28 mg. per kilogram) administered intravenously on the diameter of the pial arteries, blood pressure (*B. P.*) and spinal fluid pressure (*C. S. F.*) after recovery from ether anesthesia. Intravenous caffeine caused an acute constriction in the artery followed by a dilatation. The spinal fluid pressure (*C. S. F.*) dropped slightly and then rose. The blood pressure dropped during the administration. In the second experiment, the drop was preceded by a sudden rise in blood pressure (*B. P.*) due to a sudden movement on the part of the animal.

this particular experiment this acute rise was presumably due to a sudden movement of the animal's leg when the drug was introduced. It is the only one in the series in which it is found.

The data of all of these experiments are presented in table 5. Doses of caffeine, varying from ½ to 4 grains (0.03 to 0.26 Gm.), were used. The caffeine was introduced intravenously in all experiments excepting no. 7 in which it was given subcutaneously. In sixteen of eighteen experiments the arteries constricted for a short time (from eight to thirty seconds) after the introduction of the caffeine. The brief con-

TABLE 5.—*Effect of Intravenous Administration of Caffeine Sodio-Benzoate After Recovery from Ether**

Experiment	Dose: Caffeine Sodio-Benzoate, Grains	Dose: Caffeine, Mg. per Kilogram	Diameter of Artery, Microns: Before	Low	High	Per Cent: Low	Per Cent: High	Blood Pressure, Mm. of Mercury: Before	Low	High	Per Cent: Low	Per Cent: High	Cerebrospinal Fluid Pressure, Mm. of Ringer's Solution: Before	Low	High	Per Cent: Low	Per Cent: High
I	½	5.7	144	117	144	—19	0	46	30	58	—35	+26	34.5	34.5	36.5	0	+ 6
II	3	14.4	162	135	162	—17	0	..	..	..	....	....	42.5	35.5	49.5	—16	+17
III	2½	18.0	252	225	279	—11	+11	..	..	..	....	....	33.0	18.5	38.5	—44	+17
IV	2½	20.0	198	180	225	— 9	—14	91	51	71	—44	—22	31.0	29.0	43.0	—10	+39
V	2½	22.5	108	99	117	— 8	+ 8	65	39	71	—40	+ 9	38.0	37.5	66.5	— 1	+75
VI	2½	24.0	225	207	243	— 8	+16	94	50	150	—47	+17	37.5	33.5	37.5	—11	0
VII	2½	24.0	207	...	252	....	+22	71	39	59	—45	—17	20.5	....	44.0	....	+115
VIII	2½	24.0	171	144	180	—16	+21	94	40	..	—58	....	20.5	19.5	30.0	— 5	+46
IX	2½	24.0	189	171	180	—10	— 5	74	36	..	—51	....	7.5	5.0	22.5	—33	+200
X	2½	25.0	306	207	306	—32	0	66	40	62	—39	— 6	14.5	10.5	15.5	—28	+69
XI	2½	25.0	270	252	297	— 7	+10	38	0	60	—10	+58	40.5	....	47.5	....	+17
XII	2½	25.0	162	153	180	— 6	+11	106	78	126	—26	+19	....	....	....	....	....
XIII	2½	27.0	189	153	234	—19	+43	85	73	91	—14	+ 7	25.5	23.5	41.5	— 8	+63
XIV	2½	28.0	144	126	144	—13	0	46	38	..	—17	....	34.5	29.5	....	—15	....
XV	3	30.0	162	144	180	—11	+11	70	34	134	—51	+91	....	....	....	....	....
XVI	2½	30.0	117	...	162	....	+28	..	..	..	....	....	41.0	65.0	65.0	....	+59
XVII	3½	34.0	234	216	234	— 7	0	30	22	66	—27	+12	31.5	31.5	39.5	0	+25
XVIII	4	40.0	234	207	234	—12	0	38	30	78	—21	+11	33.5	31.5	41.5	— 6	+30

* The percentage change indicates by "low" the initial contraction of the artery, and by "high," the subsequent dilatation. The same holds true of the blood pressure and cerebrospinal fluid pressure.

striction was followed in twelve cases by a dilatation of long duration, lasting in most cases until the end of the experiment, and ranging in amplitude from 8 to 42 per cent. In one experiment the final reading was 5 per cent less than the initial value. There was considerable variation in the behavior of the artery, which probably was dependent on the depth of anesthesia. The animals more fully out of anesthesia in most cases demonstrated the acute contraction followed by a marked vasodilatation, while those showing the contraction were more deeply under anesthesia. Their behavior thus approximates that of the etherized animals.

Ether dilates the cerebral vessel, and the removal of the ether anesthesia results in a marked constriction of the vessel in most cases. This is the usual phenomenon. Often, however, one finds animals in

which, owing to some other change in the internal environment, the vessel does not contract immediately. The superficial reflexes may be present, and the animal may show signs of activity, yet the vessel remains at the ether level. Experiments 9, 10 and 14 represent such animals, and it will be noted that in these experiments caffeine exerted only a constrictor effect, which is exactly the effect exerted during ether anesthesia (table 3) when the vessel was dilated probably to its maximum. In other words, in these experiments the effect of the drug depends on the initial state of the vessel, and the knowledge of this state, whether it be initially dilated or constricted, is important before one is able to predict the action of the drug.

In table 5 are included also the data on the blood pressure and cerebrospinal fluid pressure. In most cases the cerebrospinal fluid pressure reflected the arterial diameter, decreasing as the artery became smaller and rising as the artery dilated. That this is not an absolute rule, however, is demonstrated in experiments 3, 15 and 12. Undoubtedly some of these variations can be explained as changes resulting from the animal's struggling, marked changes in acid-base rate or the result of abnormalities in respiration. It was attempted to rule these out as much as possible by using artificial respiration.

The blood pressure readings do not seem consistent on a superficial glance. In all cases but the one discussed (chart 5) there was an initial drop in blood pressure followed by a recovery to its initial value. This drop in blood pressure is presumably due to the cardiac action of the intravenous caffeine. In nine cases this sudden drop was followed by a rise in the blood pressure well above the preliminary level, lasting from five to fifteen minutes. Most of these experiments, however, did not last long enough to furnish data on the secondary effect (Sollmann and Pilcher [15]) of the drug on the cardiovascular system.

(*b*) Effects After Local Administration: Experiments were also carried out to discover the local effect of introducing caffeine sodio-benzoate directly under the window. The procedure here is exactly the same as that used in sections 1 (*b*), and 2 (*b*). The local introduction of Ringer's solution was used as a control.

In a typical experiment a female cat, weighing 4.1 Kg., was put under ether anesthesia. The experimental procedures were undertaken during the ether anesthesia. The ether was removed, and within fifteen minutes the superficial reflexes could be elicited. At this time the arterial diameter was 198 microns, the cerebrospinal fluid pressure was 44 mm. of Ringer's solution and the blood pressure was 48 mm. of mercury. The cork stoppers were removed, and 1 grain of caffeine sodio-benzoate (7.5 mg. per kilogram) was introduced under the window, and the cork stoppers were replaced. The artery began to dilate and within fifteen seconds had reached a value of 216. The spinal fluid pressure remained at a level of 44, and the blood pressure dropped slightly from the level of 48 to 44 mm. of mercury. The change in the artery lasted for two minutes, and then the artery retained its original size of 198 microns.

The results of this series of experiments are presented in table 6. In all cases but one there was a dilatation of the pial artery ranging from 4 to 34 per cent. In most cases the spinal fluid pressure remained fairly constant during the experiment. In experiment 7 it rose from 46 to 50 mm. of Ringer's solution when the caffeine was introduced, but after the syringe was removed the spinal fluid pressure remained constant while the artery dilated In all cases when the blood pressure was taken it also was constant during the entire experiment. In summary, it can be stated that the local application of caffeine to the pial artery caused a dilatation of the artery and generally no change in the cerebrospinal fluid or blood pressures. There was also a corresponding dilatation of all vessels in the microscopic field as well as an increase in the velocity of blood flow.

TABLE 6.—*Effect of Local Administration of Caffeine Sodio-Benzoate After Recovery from Ether*

Experiment	Dose: Caffeine Sodio-Benzoate, Grains	Dose: Caffeine, Mg. per Kilogram	Diameter of Artery, Microns: Before	Diameter of Artery, Microns: After	Diameter of Artery, Microns: Per Cent	Blood Pressure, Mm. of Mercury: Before	Blood Pressure, Mm. of Mercury: After	Blood Pressure, Mm. of Mercury: Per Cent	Cerebrospinal Fluid Pressure, Mm. of Ringer's Solution: Before	Cerebrospinal Fluid Pressure, Mm. of Ringer's Solution: After	Cerebrospinal Fluid Pressure, Mm. of Ringer's Solution: Per Cent
I	1	5.0	198	216	+ 9	99	99	0	50	50	0
II	1½	7.5	162	180	+12	..	..	..	70	70	0
III	1½	1.0	189	216	+14	90	90	0	42	42	0
IV	1	12.0	198	252	+27	86	86	0	29	29	0
V	1½	14.0	253	262	+ 3	35	35	0	10	10	0
VI	1½	14.0	217	217	0	61	61	0	22	22	0
VII	2	15.0	198	252	+27	86	86	0	10	10	0
VIII	1½	18.0	180	243	+35	100	100	0	20	20	0
IX	1½	20.0	216	234	+ 8	..	..	..	46	50	+8
X	1½	24.0	252	324	+28	76	76	0	40	40	0

4. *Effects of Caffeine on Animals with Low Blood Pressure.*—(*a*) Experiments During Amytal Anesthesia: In all of the experiments thus far reported the blood pressure was within normal limits. In one experiment caffeine was given intravenously just before the death of the animal during amytal anesthesia and was found to constrict the cerebral artery. This action was directly opposite to that usually found during amytal anesthesia. On investigating this unusual reaction, it was found that in this particular experiment the blood pressure had been very low. An attempt was made to evaluate this factor and to determine what effect caffeine had on the arterial diameter when the blood pressure was low. An experiment of this nature is presented in chart 6.

The cat weighed 3 Kg. and was anesthetized with 25 cc. of 1 per cent amytal intraperitoneally. During an adequate preliminary period, with artificial respiration, the size of the artery was 510 microns, and the blood pressure averaged about 72 mm. of mercury. The blood pressure was decreased by cutting the spinal cord at the third cervical level. During the laminectomy, which lasted

three minutes, and the handling of the cord preliminary to cutting, the artery retained its value of 522 microns, while the blood pressure rose to a level of 116 mm. When the cord was severed, the artery immediately dropped from 522 to 450 microns in diameter, a drop of 14 per cent, and then rose within one minute to a diameter of 504 microns. It remained at this level for twenty-four minutes,

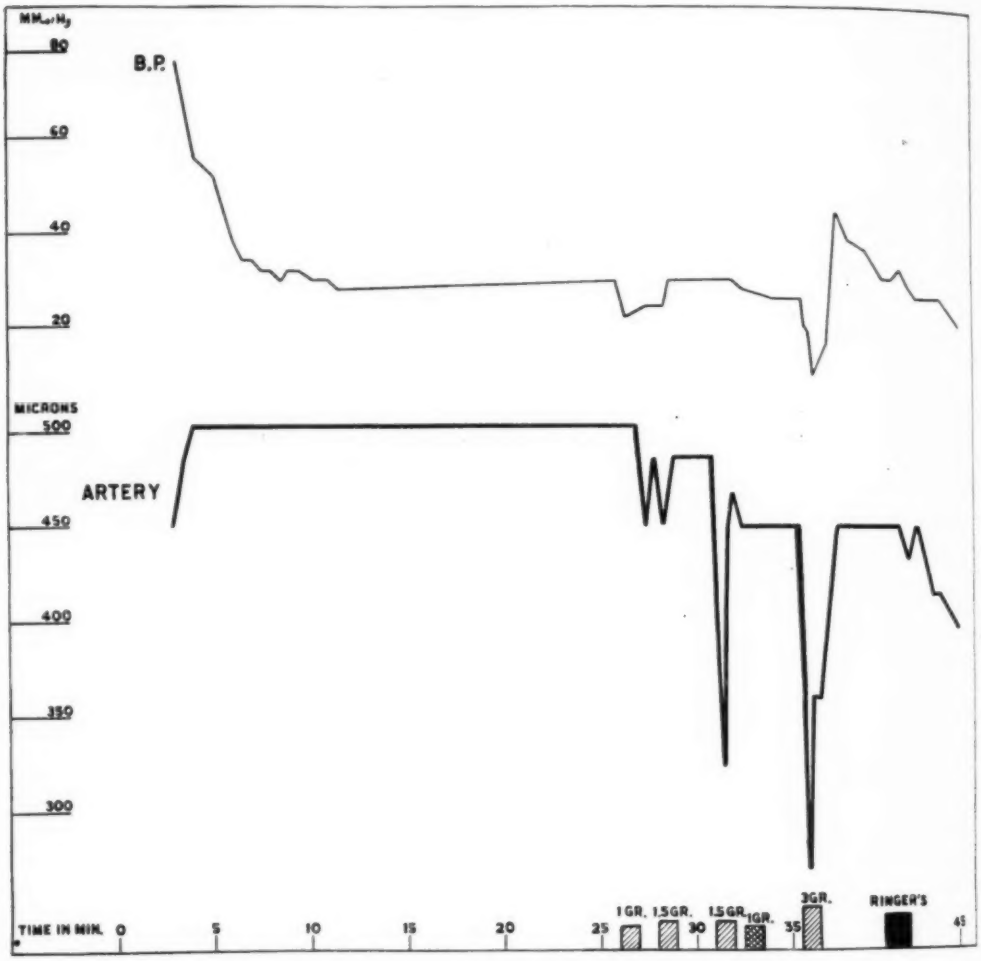

Chart 6.—Caffeine sodio-benzoate with low blood pressure; amytal anesthesia. Constrictor effect of intravenous caffeine on the pial artery in an animal with low blood pressure during amytal anesthesia. The spinal cord was cut at the third cervical level, and the subsequent changes are charted. This response is the reverse of that found with normal blood pressure during amytal anesthesia.

when caffeine was given. On cutting the cord the blood pressure dropped to a level of 38 mm. of mercury and continued to drop during the next twelve minutes until it reached a level of 14 mm., which it retained for fifteen minutes.

One grain of caffeine sodio-benzoate intravenously (11 mg. per kilogram) caused a decrease in arterial diameter from 504 to 450 microns, a decrease of 10 per cent, and within the next half minute the artery dilated to 486 microns. The blood pressure dropped from 15 to 11 mm. of mercury. At this point, 17 mg. of caffeine intravenously caused another decrease in the size of the artery from 486 to 450 microns, with very little change in the blood pressure. After both the artery and the blood pressure had returned to their preliminary level, another dose of 17 mg. intravenously, given quickly, caused an acute contraction of the artery from 486 to 324 microns with an immediate return to 486 microns, followed by a slight drop to 450 microns. The blood pressure dropped slightly, from 15 to 14 mm. of mercury. At this point 11 mg. of caffeine was injected subcutaneously. This had no effect on the size of the artery, but caused a further

TABLE 7.—*The Response of the Pial Artery to Caffeine Sodio-Benzoate in Animals with Low Blood Pressure* *

	Number of Doses	Blood Pressure, Mm. of Mercury	Dose, Grains	Mg. per Kilogram	Diameter of Artery, Microns		
					Before	After	Per Cent
Experiment A	1	28	2	10	261	198	—25
	2	28	1½	15	261	243	— 7
	3	18	2	20	180	262	—10
	4	18	2	20	189	189	0
Experiment B	1	36	2	15	324	360	11
	2	24	2	15	342	306	—10
	3	24	2	15	306	306	0
Experiment C	1	34	1½	11	90	117	30
	2	22	1	7	108	117	— 8
	3	9	1	7	117	117	0
	4	10	1	7	117	117	0
Experiment D	1	44	1	17	191	198	17
	2	20	2	34	180	180	0
	3	17	2	34	189	189	0
	4	8	1	17	189	189	0
Experiment E	1	30	1	14	524	470	—10
	2	26	1	14	506	324	—33
	3	26	1	14	450	270	—40

* Illustrating the variability in response of the size of the pial artery to the effects of intravenous sodio-benzoate in the presence of low blood pressures during amytal anesthesia. The general reaction in the presence of low blood pressure is constriction, a reverse of the normal.

drop in blood pressure. Three minutes after this, an additional intravenous injection of 22 mg. caused an acute constriction of the artery from 450 to 270 microns, followed by an almost immediate rise to 450 microns. The blood pressure took a sudden drop from 13 to 5 mm. of mercury, and then rose within the next two minutes until it reached a peak of 22 mm., from which point it fell slowly to 15 mm. At this point the flow in the artery became slow, and the artery looked cyanotic. The artificial respiration was increased, and 7 cc. of Ringer's solution was given intravenously. This had little effect, for the blood pressure continued to drop, and the artery decreased in size until the animal died.

The blood pressure in other experiments was lowered by bleeding the animal from the femoral artery. In these experiments, in the presence of a low blood pressure during amytal anesthesia, caffeine generally has a constrictor effect that is the reverse of that usually observed. This

is generally the case, but is not an absolute rule. Occasionally it has no effect on the size of the artery (table 7). The point of interest is that the same instability found in the blood pressure response to various stimuli after the introduction of caffeine with low blood pressure (Sollmann and Pilcher[15]) is also found in the behavior of the cerebral artery. Undoubtedly, one is dependent on the other. In evaluating the influence of any drug on the cerebral vessels, it is essential that the initial blood pressure be within the normal limits.

COMMENT

These experiments show that caffeine sodio-benzoate, caffeine citrate and caffeine chloride, when administered either intravenously or subcutaneously, act on the cerebral vessels. During amytal anesthesia all doses that have any effect on the vessel give a vasodilatation and an increase in the rate of blood flow. This holds true of all vessels measured, even down to arterioles 9 microns in diameter. The hyperemia of the entire field and the increased velocity of the blood returning in the venules suggest that there is also a dilatation of capillaries. The administration of caffeine intravenously during ether anesthesia has resulted in all cases in a decrease in caliber of the arteries measured. In the third series of experiments, after recovery from ether when the superficial reflexes had returned, caffeine in most cases gave a slight constriction followed by a dilatation. Studies on the direct effect of caffeine applied locally to the pial vessels show that during amytal anesthesia caffeine caused a dilatation of all the vessels; during ether anesthesia caffeine had no direct effect on the artery, while after recovery from ether it caused a dilatation. In other words, the effect of the caffeine both systemically and locally was dependent on the anesthesia used.

In other studies it has been shown that both ether and amytal anesthesia cause a dilatation of the cerebral vessel, ether causing a much greater dilatation. When caffeine is introduced intravenously, its effect will be dependent partly on the status of the blood vessel at the time when the caffeine is introduced. When the vessel is dilated moderately, as during amytal anesthesia, caffeine will cause an additional dilatation, depending roughly on the amount of caffeine used. During ether anesthesia, however, when the artery is dilated to an extreme degree it responds to caffeine by contraction. In the recovery experiments, which more closely approximate normal, the initial size of the vessel is smaller than during amytal or ether anesthesia. In this series the response in most cases consisted of a slight constriction followed by a dilatation. In five experiments, in which constriction on removal of ether did not take place and the artery retained its maximum dilatation, even though the anesthesia had been removed, the response to caffeine

was the same as during the series of experiments with ether. When the artery was moderately dilated, caffeine caused further dilatation. When the artery was extremely dilated, caffeine caused a constriction; when the artery was relatively in a normal status, caffeine caused a slight constriction followed by a dilatation. In all types of experiments the blood pressure reacted in the same way. One must conclude that the initial state of the cerebral artery is a determining factor in its response to caffeine and undoubtedly to other drugs as well. The type of anesthesia is significant only so far as it determines the size of the vessel.

Local administration of caffeine to the pial vessels in animals during amytal anesthesia and in those that had recovered from ether anesthesia demonstrated that the direct effect of caffeine is to cause a dilatation under these conditions. There is abundant experimental work showing that caffeine applied directly to vessels causes a vasodilatation. Undoubtedly the vessel responds to the caffeine in the blood stream after intravenous injection, and the dilatation could be explained on that basis. Cutting the vasoconstrictor fibers to the blood vessels in the cervical sympathetic trunk on both sides has had no effect on these reactions. The dilator fibers to the vessels have not been cut because their course has not been completely worked out.

It is not clear why the vessel should, during ether anesthesia, constrict after the intravenous injection of caffeine. Sollmann and Pilcher [15] pointed out that in excised kidneys caffeine could cause no further dilatation, but it was able to inhibit the constrictor action of epinephrine. Their perfusion experiments showed that caffeine caused a central vasomotor stimulation, which was often masked by a peripheral vasomotor paralysis. However, it is impossible to explain the constrictor effect during ether anesthesia on the basis of central stimulation, because the constrictor effect is present even after the cervical sympathetics have been cut. It might be conceivable that caffeine during ether anesthesia stimulated the postganglionic fiber or the nerve ending in the vessel. This type of stimulus was overshadowed by the local dilator effect during amytal anesthesia and after recovery when the initial size of the vessel was smaller, but the work of Fredericque [20] and his collaborators tends to prove that caffeine acts as a paralysant of the sympathetic fiber. At present this constriction during ether anesthesia cannot be explained.

In most of the recovery experiments, after ether had been removed and the superficial reflexes had returned, caffeine, when administered intravenously, caused an acute constriction followed by a dilatation. The constriction took place immediately on the intravenous introduction of the caffeine, lasted from fifteen to thirty seconds and was then followed by a dilatation. This was found to occur even after the cervical sympathetics were cut, removing the possibility of central preganglionic

stimulation. Hence, the constriction cannot be explained according to Sollmann and Pilcher [15] on a basis of central stimulation. In all these experiments but one, as well as in the experiments with amytal and ether, the intravenous injection of caffeine caused an acute drop in blood pressure, cardiac in origin (Sollmann and Pilcher [15]). This drop in blood pressure lasted from fifteen seconds to a minute and was followed by a prompt recovery. Wolff and Blumgart [60] mentioned that narrowing of the pial vessels occurred when there was a conspicuous drop in blood pressure. It seems probable that the intravenous introduction of caffeine in normal animals causes an acute narrowing of the pial vessel due to the sudden drop in blood pressure. When the blood pressure had recovered and caffeine was circulating in the blood stream, the cerebral vessels dilated as the result of the active local effect of caffeine in the blood stream. The fact that this preliminary narrowing was not observed when caffeine was introduced locally under the window would show that it is due to some systemic mechanism. Such a preliminary constriction has been reported with caffeine by Beco and Plumier [22] and Morimoto.[23]

Why was this preliminary constriction not observed in the experiments with amytal and ether? Both amytal and ether cause vasodilatation in the cerebral vessel, when given to the animal after recovery from ether anesthesia; therefore, it seems that the anesthesia must cause an inhibition of this preliminary constriction. In other experiments, to be published, it was noted that the preliminary constrictor effect can be observed when large doses of caffeine are given to animals during very light amytal anesthesia, i. e., about one-half the usual dose. This additional evidence points to the possibility that the preliminary contraction associated with the abrupt drop in blood pressure can be inhibited by amytal anesthesia.

The experiments of Forbes and Wolff [61] have shown that as a rule the cerebrospinal fluid pressure goes hand in hand with the size of the artery. When the artery dilates, the blood volume in the brain is increased, and this is reflected by a rise of spinal fluid pressure in the cistern manometer. Likewise, when the artery constricts the spinal fluid pressure drops. In the present series of experiments this relationship holds fairly constantly. In the experiments with amytal, in which there

60. Wolff, H. G., and Blumgart, H. L.: The Cerebral Circulation: VI. The Effect of Normal and of Increased Intracranial Cerebrospinal Fluid Pressure on the Velocity of Intracranial Blood Flow, Arch. Neurol. & Psychiat. **21**:795 (April) 1929.

61. Forbes, H. S., and Wolff, H. G.: Cerebral Circulation: III. The Vasomotor Control of Cerebral Vessels, Arch. Neurol. & Psychiat. **19**:1057 (June) 1928.

was invariably a dilatation of the artery, there was a rise in spinal fluid pressure. In the other experiments in which there was a constriction of the vessel from its dilated level, the cerebrospinal fluid pressure dropped in all cases. In the experiments after ether anesthesia the cerebrospinal fluid pressure reflected the arterial size less accurately. One is inclined to attribute the discrepancy to the experimental conditions. Often the animals would move voluntarily or would take several deep breaths, which would be reflected in the cerebrospinal fluid readings much more readily than in the arterial diameter or blood pressure readings. The conditions for the accurate measurements of these factors were much better in the experiments with amytal and ether than in those made after ether had been removed.

The recent work of Stevenson, Christensen and Wortis,[30] and of Denkers [31] shows that in unanesthetized patients caffeine sodio-benzoate caused a decrease in cerebrospinal fluid pressure. Denkers explained this primarily on the basis of the diuretic effects of caffeine. Denkers found that the greatest drop in pressure occurred after the first five minutes. One is inclined to believe that if diuresis were the most important mechanism the drop in spinal fluid pressure would not occur so soon after the injection and would persist longer.

In all probability their results could more reasonably be explained on the basis of the action of caffeine on the respiratory mechanism. It has been shown (Binz,[33] Cushny,[62] Higgins and Means [63] and Smith [64]) that caffeine acts as a respiratory stimulant, causing an alkalosis, which in turn was shown by Wolff and Lennox [65] to cause a vasoconstriction. It is most probable that this vasoconstriction is reflected by a drop in cerebrospinal fluid pressure. In these experiments with caffeine the anesthesia, and in some cases artificial respiration, may have prevented the alkalosis; thus, these results are more specifically due to the circulatory effect of caffeine. Denkers did not state the exact dose per kilogram of body weight of caffeine used, but in all probability it was not great enough to cause a change in blood pressure.

The effect of caffeine on blood pressure in all types of experiments is of interest. During amytal and ether anesthesia the blood pressure dropped acutely and then returned to its normal level. As a rule, the drop was greater when larger doses were used. This is in keeping with the results of Aubert,[40] Maki,[41] von Schroeder,[11] Philips and Brad-

62. Cushny, A. R.: J. Pharmacol. & Exper. Therap. **4**:363, 1913.

63. Higgins, H. L., and Means, J. H.: J. Pharmacol. & Exper. Therap. **12**:1, 1915.

64. Smith, R. G.: J. Pharmacol. & Exper. Therap. **33**:147, 1928.

65. Wolff, H. G., and Lennox, W. G.: Cerebral Circulation: XII. The Effect on Pial Vessels of Variations in the Oxygen and Carbon Dioxide Content of the Blood, Arch. Neurol. & Psychiat. **23**:1097 (June) 1930.

ford,[16] Vinci,[36] Gottlieb and Magnus,[18] Loewi, Fletcher and Henderson[19] and Sollmann and Pilcher.[15] However, a slight rise following this drop during amytal and ether anesthesia was not found. In the animals recovered from ether anesthesia there was an acute drop followed by a rise. Sollmann and Pilcher[15] have shown that the acute drop in blood pressure was due to the direct effect of caffeine on the cardiac muscle, causing cardiac depression. This cardiac depression was followed by a mild cardiac stimulation that would cause a permanent mild rise in blood pressure, especially when small or moderate doses were used. Most of these experiments were of too short duration to offer data on the permanent effects of caffeine sodio-benzoate. Here it can be stated that both amytal and ether anesthesia inhibited the secondary rise in blood pressure, which Sollmann and Pilcher[15] showed occurred with small and moderate doses. This rise was found, however, in many of the experiments after recovery from ether.

The local experiments during amytal anesthesia and after recovery from ether demonstrated a definite vasodilatation of the arteries and veins; the whole microscopic field appeared redder. There was no change in the blood pressure readings when taken. The spinal fluid pressure rose in some cases, owing to pressure exerted in introducing the caffeine under the window. The dilatation of the artery is due to the direct action of caffeine sodio-benzoate on the vessel wall or its nerve endings; this is in keeping with the results of most investigators. With ether anesthesia, however, the vessel was in a state of rather extreme dilatation to begin with; so caffeine applied locally had no effect on the caliber of the vessel. This definitely illustrates the importance of the preliminary state of the vessel in relation to its reactivity to drugs. The same situation was encountered by Forbes and his associates[59] in their study of histamine. The reaction of the drug was dependent on the initial status or tone of the vessel.

By this technic, it was possible to measure arterioles down to a magnitude of 9 microns. These reacted in the same way as did the larger arterioles and arteries. In several experiments measurements were made of veins and venules. In general, it is true that the veins reacted in the same way as the arteries, but not to quite the same degree. There is at present no quantitative measurement of the capillaries, but on both local and intravenous administration of caffeine during amytal anesthesia and after recovery from ether anesthesia, there was a reddening of the entire microscopic field. There were observed an increased velocity of flow and a dilatation of the veins and venules as well as of the arteries and arterioles. These facts lead to the inference that the capillaries, as well as the arterioles and venules, dilated. The increase in velocity went hand in hand with vasodilatation. The cere-

brospinal fluid pressure for a moment approached the level of the arterial blood pressure, which, according to Wolff and Blumgart,[60] should cause a decrease in velocity. These experiments offer no quantitative measurement of the change in velocity, and the observation is merely reported. Landegren and Tigerstedt[66] reported that caffeine causes an increase in the velocity of blood flow. More recently, Karger,[67] Pethe[68] and Peritz[69] believed that caffeine, by increasing the blood flow, was beneficial in the treatment of epilepsy.

Sollmann and Pilcher[15] believed that caffeine stimulated the "vasomotor" (? vasoconstrictor) center. These experiments do not confirm this observation so far as the constrictor impulses to the blood vessels are concerned. The results were the same even when the cervical sympathetic chains in the neck were cut. On the contrary, two experiments convinced Fredericque that caffeine acted as a paralysant to the sympathetic fiber. Caffeine caused an inhibition of the vasoconstriction that follows faradic stimulation of the central end of the cervical sympathetic trunk. This paralysis may play some rôle in the dilatation of the vessel. That caffeine has a direct effect on the vessel wall itself in excised vessels has been shown by Cow.[21] Probably the dilatation of the vessel is the result of several factors, one being the direct action on the vessel itself, and another the paralysis of the sympathetic end-organ in the wall of the vessel.

These experiments in no way lend support to the idea of Dreikurs[56a] on the action of caffeine. He believed that the action of caffeine was dependent on the autonomic status of the patient. When the action of the vagus was predominant, caffeine acted on the vagus mechanism. Likewise, in other patients in whom the sympathetic action predominated, caffeine reenforced this mechanism. In these experiments the action on the vessel was exactly the same whether the cervical sympathetics were intact or cut. It is obvious that cutting the sympathetics allows the vagus dilator mechanism to act predominantly, and one would expect a different reaction than when the sympathetics were intact. This was not found to be the case.

The type of response to caffeine in the presence of low blood pressure is of interest from several points of view. It was found that with low blood pressure during amytal anesthesia caffeine most frequently gave a reversal of the usual dilatation. Often it caused no reaction on the part of the blood vessel. This again emphasizes the importance of

66. Landegren, E., and Tigerstedt, R.: Skandinav. Arch. f. Physiol. **4**:241, 1892.

67. Karger, P.: Deutsche med. Wchnschr. **50**:1531, 1924.

68. Pethe, F.: Budapesti orvosi crypog. **23**:255, 1925; quoted by Lennox, W. G., and Cobb, S.: Epilepsy, Harvard Medicine Monographs, Baltimore, Williams & Wilkins Company, 1928, vol. 14.

69. Peritz, G.: Ztschr. f. d. ges. Neurol. u. Psychiat. **102**:395, 1926.

the preliminary status or tone of the circulatory apparatus in considering any vascular reaction. Sollmann and Pilcher [15] have pointed this out, and these experiments add confirmatory evidence. Whether one is observing the blood pressure or the caliber of the artery, the response is definitely conditioned by the initial status of the system. Undoubtedly a great deal of the divergence of opinion in circulatory and pharmacologic problems arises from the lack of consideration of this fundamental fact.

Do the vessels in the pia react in the same way as do the vessels in the rest of the body? A review of the literature showed that the preponderance of evidence pointed to the fact that caffeine caused a vasodilatation, often preceded by a slight constriction. This slight constriction was found present when the drug was given intravenously and can be explained most reasonably on the basis of acute cardiac depression. However, the direct application of caffeine to the wall of the vessel causes a vasodilatation. This was found to exist in the vessels of muscle, kidney, retina, lung and liver. These experiments demonstrate the same reaction in the cerebral vessels of the pia. As yet there is no direct evidence of the action of caffeine on the deep vessels in the parenchyma of the brain. The fact that the velocity of the blood is increased in the arterioles entering the parenchyma of the brain and in the venules coming out of the parenchyma would lead one to believe that in all probability the deep vessels also dilate. In general, the results of these experiments on the pial vessels are in keeping with the results of most investigators studying vascular response to caffeine elsewhere in the body.

SUMMARY

1. During amytal anesthesia the intravenous administration of caffeine sodio-benzoate caused a dilatation of the pial artery, a rise in cerebrospinal fluid pressure and an abrupt drop in blood pressure with immediate return to normal. Local administration of caffeine solution to the pia caused a dilatation of the pial artery and in most cases no change in cerebrospinal fluid pressure or blood pressure.

2. During ether anesthesia the intravenous administration of caffeine caused a constriction of the pial artery from its initial diameter, a drop in cerebrospinal fluid pressure and an abrupt drop in blood pressure with return to normal. After local administration, during ether anesthesia, caffeine had no effect on the pial artery and in most cases caused no change in the cerebrospinal fluid pressure and blood pressure.

3. After recovery from ether anesthesia, when the superficial reflexes were present, the intravenous administration of caffeine caused an acute constriction of the pial artery followed in most cases by an

immediate dilatation. In most cases the cerebrospinal fluid pressure dropped and then rose immediately. The blood pressure dropped abruptly and then immediately rose to its normal level, and in most cases exceeded its preliminary level. Local administration of caffeine solution to the pia, after recovery from ether, caused a dilatation in the pial artery with no change in most cases in the cerebrospinal fluid pressure or blood pressure.

4. In cats with abnormally low blood pressure during amytal anesthesia, caffeine sodio-benzoate, when administered intravenously, caused a marked variability of response in the pial artery. In most cases the caffeine caused a constriction of the pial vessel, which is the reverse of what is found when the blood pressure is within normal limits.

5. The response of the pial vessel to caffeine was dependent on the initial diameter of the artery before the caffeine was introduced.

6. During amytal anesthesia and after recovery from ether anesthesia, there was evidence of dilatation of the measurable arteries, arterioles and venules. Changes in velocity and color were observed, which indicate that the caffeine caused a dilatation of the capillaries as well.

7. The results presented are in keeping with the results of most investigators studying the vascular response to caffeine in other parts of the body. This would suggest that the vessels of the pia respond to caffeine in the same way as do the vessels elsewhere in the body.

Dr. Stanley Cobb extended encouragement throughout the course of these experiments, and Dr. Henry S. Forbes rendered assistance in working out the technical details.

ENCEPHALOGRAPHY

ANATOMIC AND CLINICAL CORRELATIONS

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The development of encephalography has provided a new method of precision for the examination of organic diseases of the brain. During the past three years we have used this procedure in five hundred and three cases and have found it of great value in the interpretation of symptoms and prognosis. This procedure, while not devoid of dangers, if carefully used gives information concerning the nature and extent of cerebral pathologic conditions which offsets the hazards involved.

The interpretation of the roentgen shadows in the encephalogram is dependent on the physical relations existing in the skull. Collections of air replacing fluid-filled areas result in the facilitation of the passage of the x-rays. In the normal encephalogram one finds a constant general pattern of cerebral topography. This is subject to alteration by various pathologic processes especially common in dementia paralytica, as shown by inflammatory arachnoiditis and atrophic changes.

In the normal brain the cerebrospinal fluid spaces show clearcut anatomic relationships. Any extensive alterations of these anatomic relationships result in distortion, obliteration or displacement of the cerebrospinal fluid pathways replaced by air. Many clinicians have been skeptical of the interpretation of encephalograms.

In these studies we have attempted to reconstruct the cerebrospinal fluid pathways in relation to the normal brain by direct injections of wax, thus obtaining a cast of the internal communicative pathways.

In the dissection of the normal brain there are many passageways that apparently remain potential until some pathologic change develops. We present some of these changes in visualization as contrasted with actual anatomic plates. Our clinical material and characteristic encephalographic observations are summarized in the accompanying table.

In the normal encephalogram, the distribution of air is dependent on the replacement of fluid of the ventricular system and of the extracerebral spaces, wherein the fluid is limited by the dura which passes

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over the most prominent points of anatomic structure. As the dura is not turned in to conform to the lesser variation in contour, this space becomes filled with fluid. There is in the normal brain patent communication between most of these spaces. It has been our attempt to point out the more important of these spaces and the communication between them by using anatomic models for comparison with the encephalogram,

Diagnosis	No. of Patients	Total No. of Encephalograms	General Findings
Dementia paralytica	107	173	Varying degrees of enlargement of ventricles with cortical atrophy or arachnoiditis; dilatation of basal cisterna, often including the cisterna vena magna; accessory pathways, especially in the region of the sylvian fissure; localized separation from the meninges; separation in the region of the longitudinal fissure; after malaria, resolution of the arachnoiditis in areas; visualization of a much more extensive atrophy; occasional ventricular collapse; cisternae and ventricles continue dilated; widened sulci throughout and loss of structure visualized
Before malaria..	...	86	
After malaria....	...	87	
Tabes dorsalis.....	6	10	In all of the tabetic cases in which injections were made, the process seemed to involve the brain with a low grade reaction with organization, giving clear visualization of atrophy with little arachnoiditis; ventricles usually small and distorted; deep cortical fissures altering the cerebral typography
Posttraumatic.....	19	24	Localized atrophy with ventricular dilatation on the side of injury; widened cortical sulci; alteration in cerebral topography (fracture demonstrated); without fracture; lateral areas of detachment from dura; separation of medial longitudinal sulci; generalized atrophy with increased fluid over cortex
Epilepsy.....	78	116	Dilatation of basal cisterna, often including the cisterna vena magna; some arachnoiditis; in some cases low grade atrophy with increase of fluid in pockets over cortex and dilated ventricles; normal findings; posttraumatic or postinfective; cortical atrophy with localized collections of fluid; dilatation of basal cisterna, often also of the cisterna vena magna; idiopathic findings; slight to moderate dilated basal cisterna with occasional visualization of cisterna vena magna; low grade arachnoiditis, tumors, etc., characteristic findings of this pathologic condition
Mental deficiency....	15	21	Variable picture; localized atrophy; unilateral ventricular enlargement frequent; bilateral ventricular enlargement in some; dilatation of basal cisterna; almost always marked convolutional atrophy with deepening and widening of sulci

thus indicating the anatomic structure limiting these spaces, which structure, by pathologic variation, gives altered and better visualization. We have attempted to use, so far as possible, the anatomic terminology in describing these spaces.

The committee for the standardization of encephalography, as quoted by Pendergrass, has given a clearcut description of the findings in the normal encephalogram, and many other workers have contributed to the interpretations involved, such as Penfield, Waggoner, Woods, Pancoast and Fay, Dandy, Bingel, Martin and Uhler, Meyer and others.

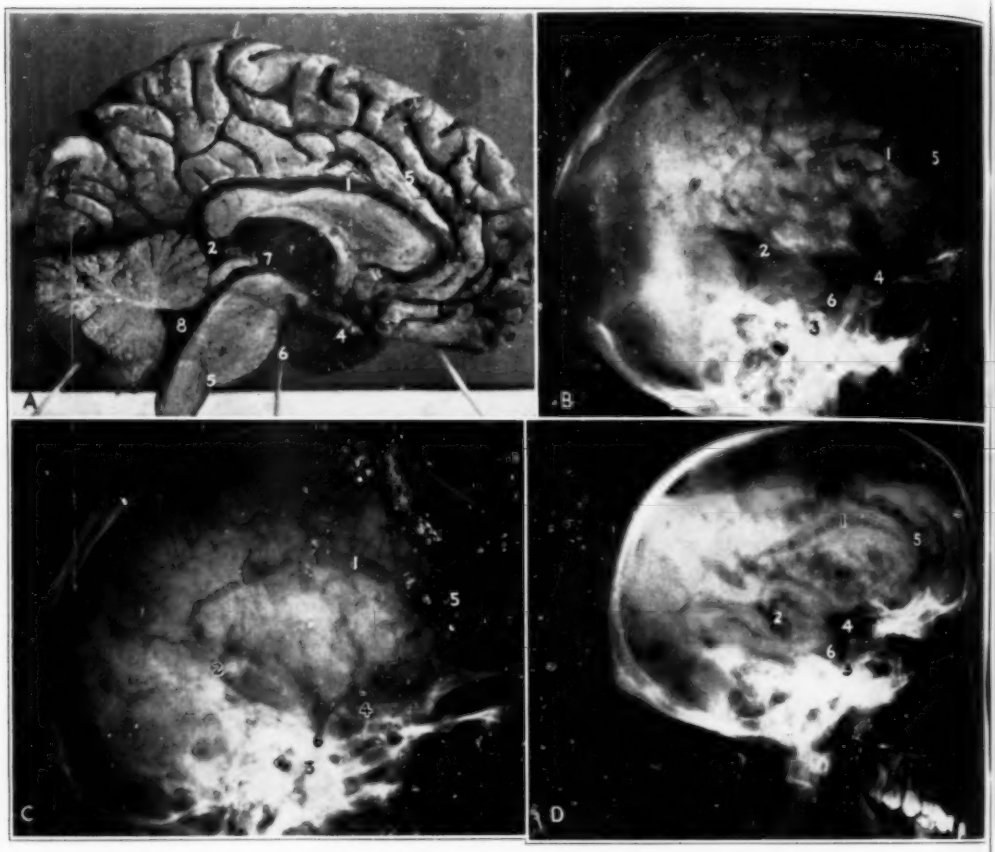

Fig. 1.—Cisterna longitudinalis cerebri. *A*, normally, this space is not filled by air to the extent of visualization, but with the occurrence of certain pathologic events it is readily visualized. From anatomic studies we are convinced that the filling is from the cisterna pontis by way of the cisterna peduncularis and extension of the posterior cerebral artery. This space lies between the artery of the falx and the corpus callosum (top arch), limited posteriorly by the crus of the fornix anteriorly. *B*, visualization by block of the internal system to air without arching, characteristic of increased internal pressure. *C*, visualization of this pathway by blocking of the internal passages by a verified tumor of the fourth ventricle. Note the raising of the central arch by dilatation of the ventricles and an absence of the shadow of the fourth ventricle. *D*, visualization of this space by ventricular collapse. This space is supported by the band of the corpus callosum and the structure of the thalamus. A case of dementia paralytica with marked atrophy and arachnoiditis. *1* indicates the cisterna longitudinalis cerebri, *2*, the cisterna interpeduncularis with extension; *3*, the cisterna pontis; *4*, the cisterna chiasmatis; *5*, the sulci cinguli; *6*, the anterior border of the pons; *7*, the third ventricle; *8*, the fourth ventricle.

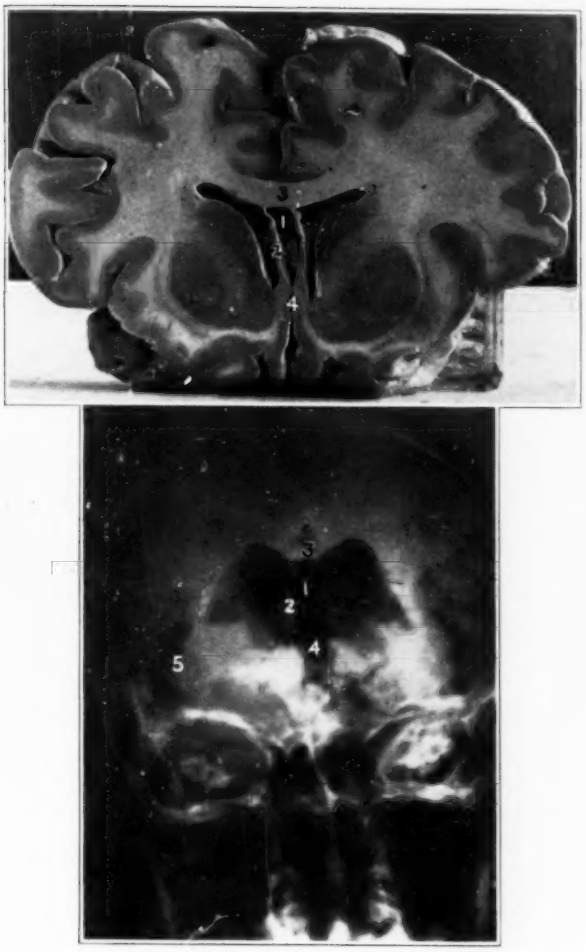

Fig. 2.—Visualization of the fifth ventricle. The so-called fifth ventricle is an anatomic variant occurring occasionally in brains that are otherwise normal. When this picture is presented, the columns of the fornix and the septa pellucida are widely placed, giving a rather extensive cavity between these structures. Fluid replacement occurs through a small patent opening in the tip of the third ventricle, which communicates directly with this space. The structures seen are as follows: *1*, the fifth ventricle; *2*, columns of the fornix; *3*, the corpus callosum; *4*, the third ventricle, and *5*, the insula.

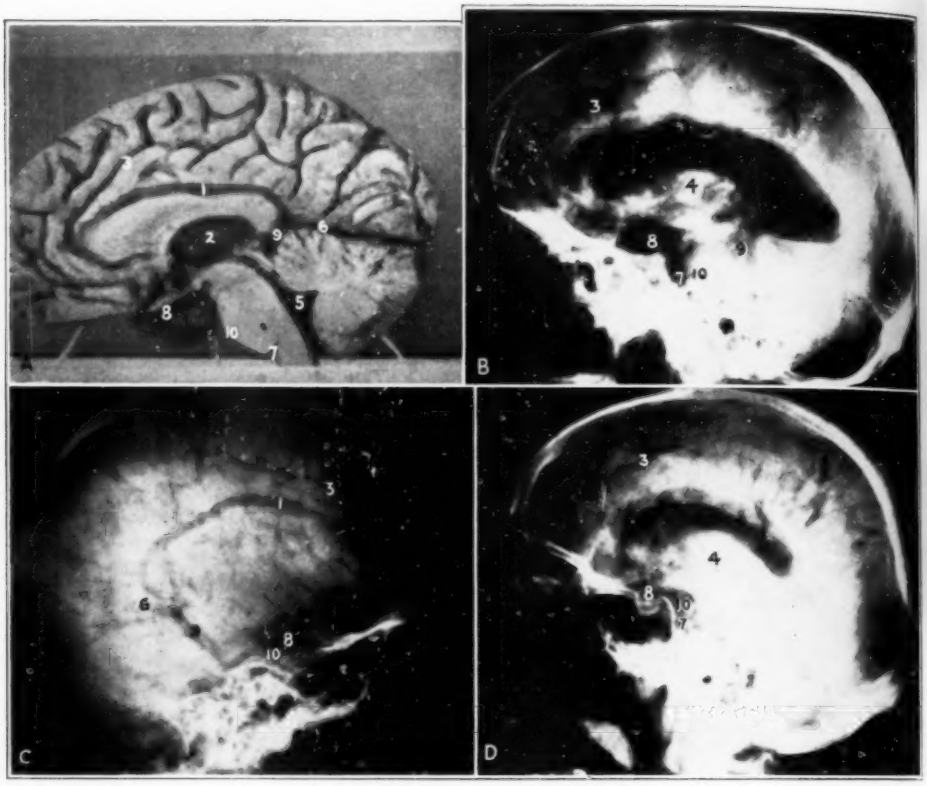

Fig. 3.—The sulci cinguli. *A*, filling of this sulcus occurs to a notable extent in cases of severe atrophy. It is also visualized in practically all cases in which the stria longitudinalis is filled, probably by direct transmission of air from this space. *B*, a case of severe atrophy of dementia paralytica. The anterior part of the cingulum is largely destroyed in this case. The communication here is apparently anterior through the extent of the sulci cinguli. *C*, filling of the sulcus cinguli in a case of fourth ventricular block associated with filling of the stria longitudinalis. *D*, a lesser degree of atrophy of dementia paralytica with the arachnoid process largely obliterating the cortical pathways. Here the sulcus cinguli is apparently filled by the communication from the anterior interhemispheric pathway made patent by atrophy. *1* indicates the cisterna longitudinalis cerebri; *2*, the third ventricle; *3*, the sulcus cinguli; *4*, the body of the thalamus; *5*, the fourth ventricle; *6*, the cisterna vena magna; *7*, the cisterna pontis; *8*, the cisterna chiasmatis; *9*, the cisterna interpeduncularis with extension along the course of the posterior cerebral artery; *10*, the anterior border of the pons.

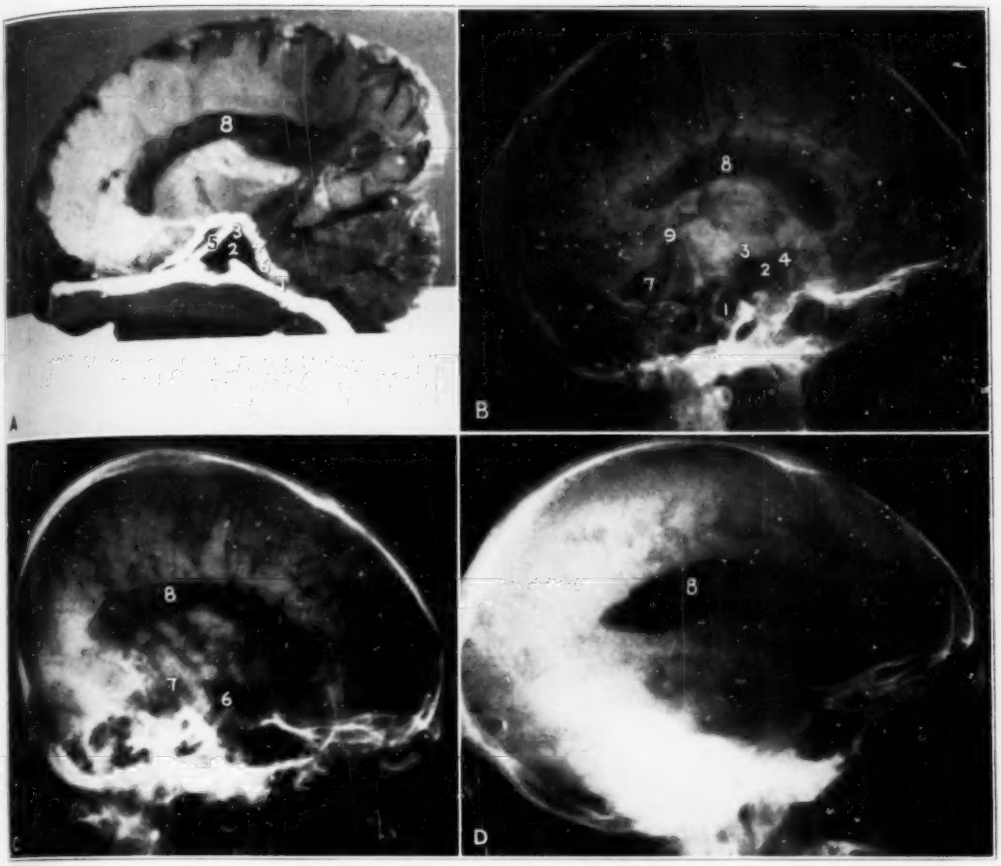

Fig. 4.—The cisternae chiasmatis, interpeduncularis and pontis; visualization of the optic tract. *A*, the fluid issuing from the fourth ventricle by way of the foramina of Luschka and Magendie communicates with the cisterna vena magna, being limited in this space by the dura against the atlantoid ligament. The space is limited anteriorly by the brain stem and superiorly by the inferior surface of the cerebellum. Communicating pathways pass around the brain stem at the inferior border of the pons, ending in a space formed by the passage of the dura directly over the notch between the lower border of the pons and the brain stem. Superiorly, this space extends around the body of the pons, and here it communicates with a space limited superiorly by the structure of the thalamus and its pial covering; laterally it is limited by the medial surface of the temporal lobes, and anteriorly, by the limits of the medial cranial fossae. Posteriorly, it is limited by the pons and cerebral peduncles. This space contains the optic chiasm and has been termed the cisterna chiasmatis. It communicates directly through the cisterna interpeduncularis with the space around the posterior cerebral artery and also with the temporal fissure. As it communicates with the sylvian fissure, it is the main pathway for the passage of fluid over the cortex. Any process interfering with the normal cortical distribution of the fluid is a factor in causing dilatation of the cisternae chiasmatis and interpeduncularis. Atrophic processes are also usually accompanied by dilatation of this space. *B*, marked dilatation of the cisterna pontis; visualization of the anterior border of the pons in a case of generalized atrophy in early tabetic dementia paralytica. *C*, dilatation in general atrophy and arachnoiditis in dementia paralytica. Note the optic tracts and the anterior border of the pons. *D*, marked dilatation and communication into the interhemispheric space by way of the anterior fossa, in dementia paralytica with marked arachnoiditis. *1* indicates the cisterna pontis; *2*, the cisterna chiasmatis; *3*, the thalamus; *4*, the interpeduncularis; *5*, the optic tract; *6*, the anterior border of the pons; *7*, the fourth ventricle; *8*, the lateral ventricle; *9*, the aqueduct of Sylvius.

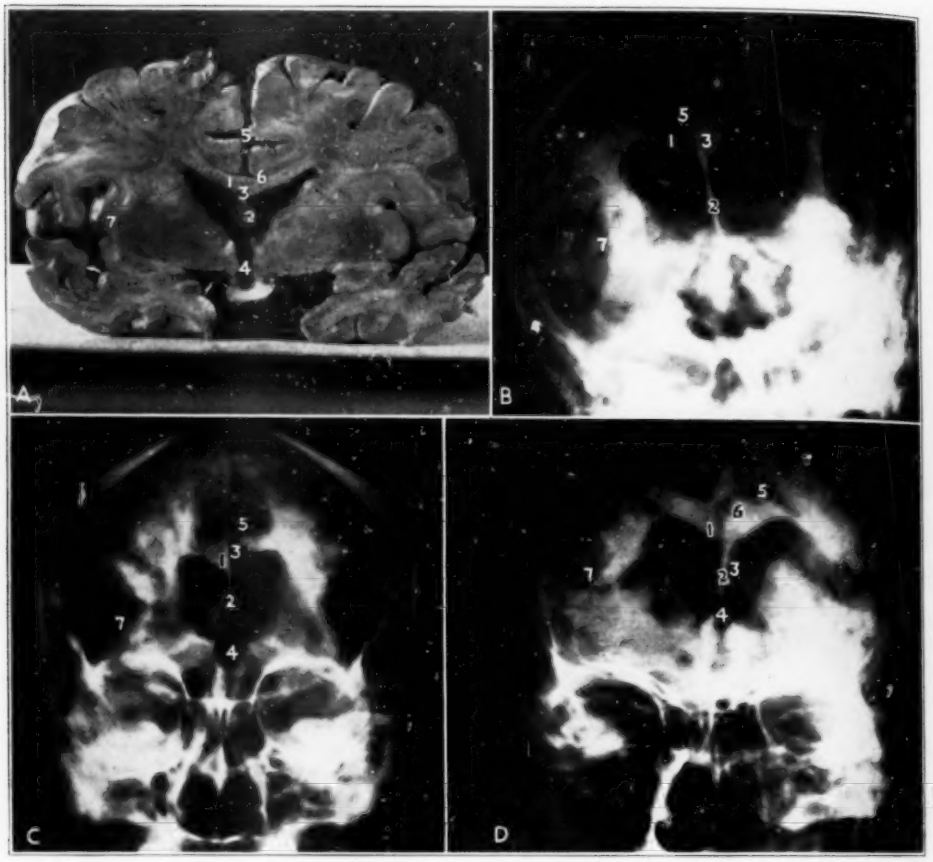

Fig. 5.—Cavity of the septum pellucidum. *A*, in the normal brain, except in anomalies wherein there is a wide separation of the columns of the fornix, this space is rarely filled. This space is formed by the two laminae of the septum pellucidum and normally is not visualized in encephalography. In two conditions, however, it contains sufficient air for visualization. In the congenital anomaly (fifth ventricle) the septums are widely placed, and there is a patent opening from the tip of the third ventricle into this space. In the severe generalized atrophy of dementia paralytica, this space is quite often visualized. Three cases are shown in which varying grades of atrophy have been visualized. In all of these cases the atrophy is marked. The filling of this space in our cases has occurred in those in which there was marked mental deterioration. *B*, in addition to visualization of the cavity of the septum pellucidum, there is marked cingular and lateral atrophy. The corpus callosum appears less dense than normal—advanced type A dementia paralytica. *C*, gross destruction of the corpus callosum along with lateral and cingular atrophy—very advanced type A dementia paralytica. *D*, the lamina of the septum pellucidum on the left seems obliterated above, with a decrease in the shadow of the corpus callosum. Lateral and cingular atrophy add to the picture of distortion—type A dementia paralytica. *1* indicates the corpus callosum; *2*, the columns of the fornix; *3*, the cavity of the septum pellucidum; *4*, the third ventricle; *5*, the sulcus cinguli; *6*, the cisterna longitudinalis cerebri; *7*, the insula.

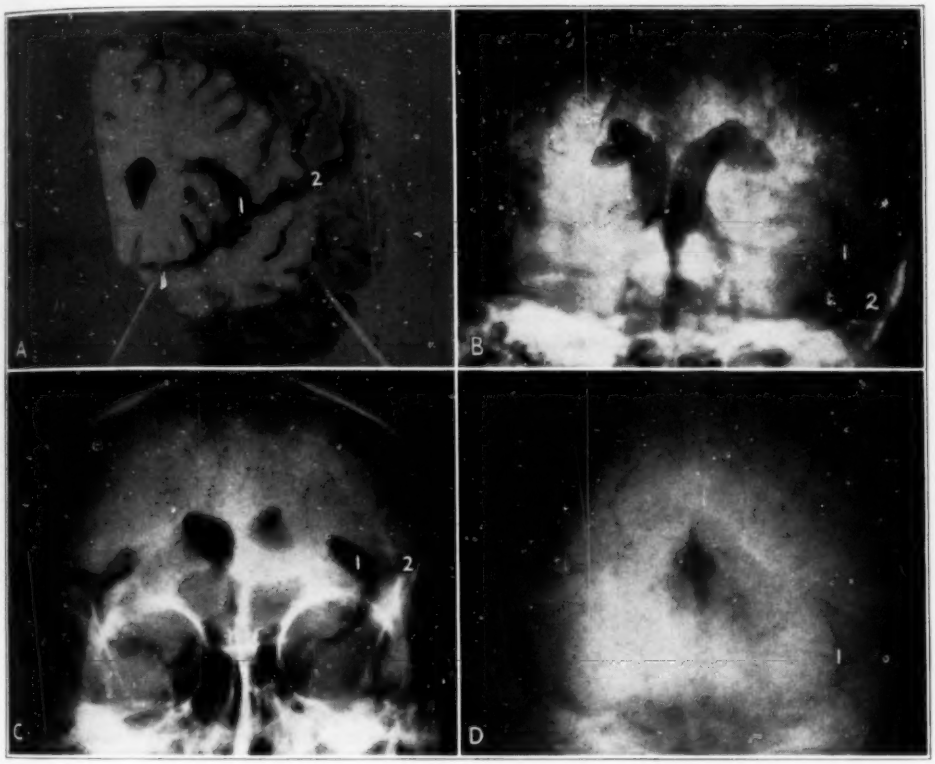

Fig. 6.—Insula visualization. *A*, the area of primitive cortex, which is overlayed by the developing pallium, has a patent communication with the sylvian fissure. In the normal encephalogram this area is not visualized. When, owing to pathologic changes, it is filled with air, it is visualized as a crescent-shaped area which is anatomically limited, inferiorly by the circular sulcus and superiorly by the overlapping pallium. Directly central lies the globus pallidus, and laterally the overlapping pallium of the parietal and temporal lobes, which is divided by the depth of the sylvian fissure. Atrophy patterns which allow for visualization are usually significant of pallidal disease. These changes are: *B*, unilateral degeneration in a case of unilateral parkinsonian syndrome; *C*, dementia paralytica with marked rigidity and tremors, showing shrinking with widening of the insular space; *D*, bilateral parkinsonian syndrome. The structures seen are: *1*, the insula, and *2*, the sylvian fissure.

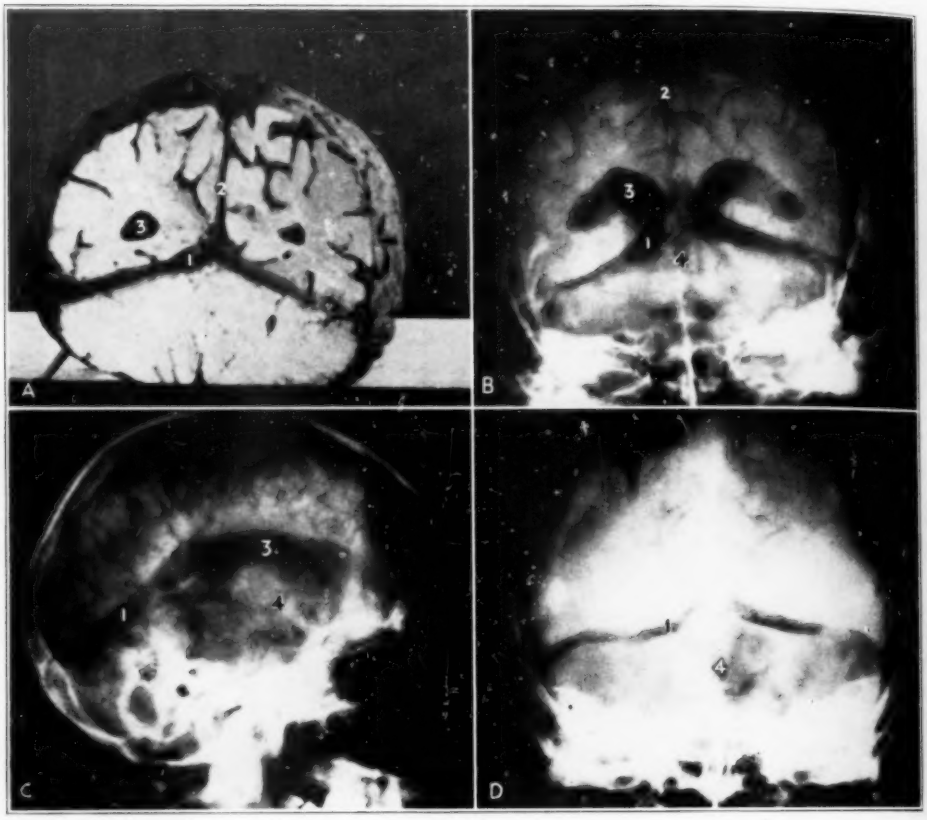

Fig. 7.—The cisterna vena magna cerebri. *A*, the air-filling of the cisterna vena magna cerebri is limited superiorly on all sides by the tentorium cerebelli, and laterally by the tentorial attachment and dural contact with the skull. Inferiorly, it is limited by the superior surface of the cerebellum. This space in the normal brain is not filled to the extent of visualization. Pancoast and Fay expressed the belief that dilatation of this space is the result of increased fluid, owing to failure of fluid absorption. We have observed its appearance most commonly in epilepsy and in dementia paralytica, in which an arachnoid pattern is present over the cortex. Several cases of dementia paralytica, which at postmortem examination have shown a markedly increased amount of fluid under the tentorium, also showed a marked inflammatory adhesive process over the superior surface of the cerebral cortex. *B* and *C*, anteroposterior and lateral views in a case of posttraumatic epilepsy, showing a clearcut cisterna vena magna as part of a generalized fluid increase with a generalized atrophic process. *D*, dementia paralytica with advanced arachnoiditis and a basal collection of fluid, which has been replaced by air. *1* indicates the cisterna vena magna; *2*, the cisterna longitudinalis cerebri; *3*, lateral ventricle; *4*, third ventricle.

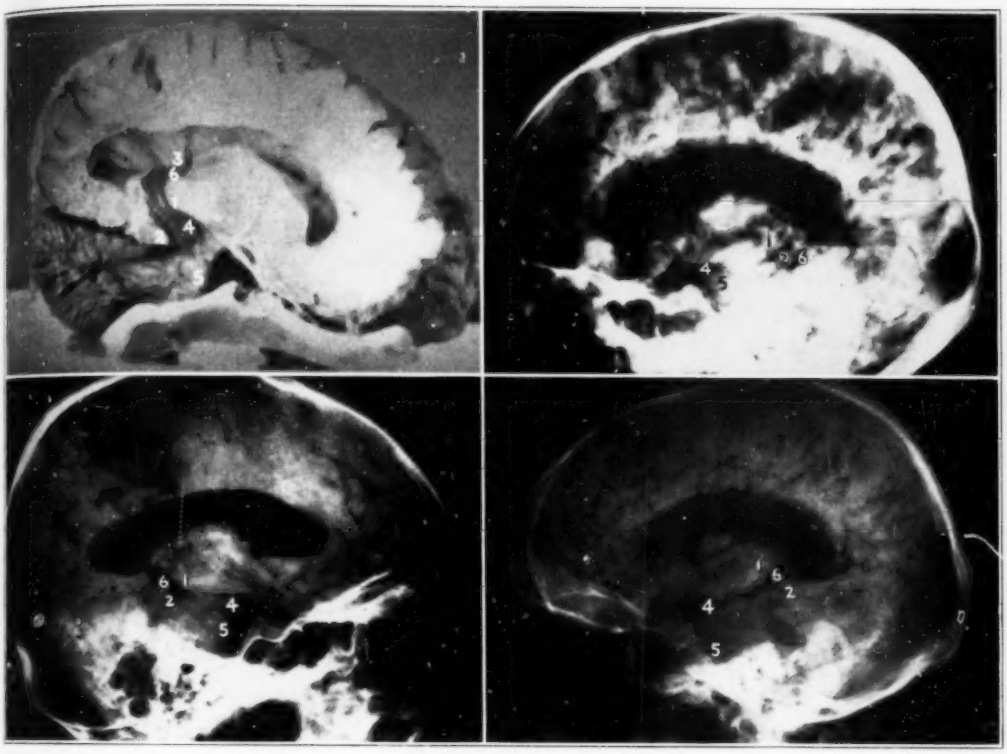

Fig. 8.—Extension of the cisterna interpeduncularis along the posterior cerebral artery into the region of the medial longitudinal fissure. In cases of low grade generalized atrophy, there is often visualized an air-filled area starting with the cisterna interpeduncularis and extending around the anterior border of the pons. It takes the course of the posterior cerebral artery; it then becomes limited laterally by the covering of the fimbria of the hippocampi, and anteriorly by the pulvinar of the thalamus. It passes up over the posterior part of the corpus callosum, ending in the sulcus of the corpus callosum, being limited superiorly by the cinguli convolutions. Three cases are shown, indicating the occurrence of this phenomenon in low grade atrophy of dementia paralytica without arachnoiditis. It is not visualized in the normal brain, and as yet we have not observed it in any condition except dementia paralytica. It tends to occur with organized atrophic processes. The patients included have shown clinical evidence of a thalamus syndrome, which is of interest, as the thalamus forms the anterior border of this space. *1* indicates the pulvinar of the thalamus; *2*, the fimbria hippocampi; *3*, the ventricular floor; *4*, the cisterna interpeduncularis; *5*, the anterior border of the pons; *6*, the extension between the pulvinar and the fimbria.

Since the origin of the method by Dandy in 1918, much progress has been made in the technic and in the interpretation of the patterns found. With the occurrence of certain pathologic events, many of the spinal fluid spaces are so altered that visualization is markedly improved. From a rather extensive series completed at this hospital, we have chosen plates that indicate clearly the structures that are shown on our anatomic models.

In our series of cases the mortality was less than 0.25 per cent. With the use of the dual needle system, we believe that the contraindications are few. Arteriosclerosis, detectable in the optic disk, meningovascular reactions (syphilis) and too great an increased pressure due to lesions of the posterior fossa are the most common contraindications. One patient with arteriosclerosis died, and in one case a hemiplegia developed following the encephalography; Rosenheck also reported a hemiplegia from this cause.

Our experience in epilepsy has been exceedingly encouraging. In using dehydration methods following the injection of air, we have had in many cases a freedom from attacks for months. We believe also that it has advantages in posttraumatic psychoses, as we have seen improvement in many cases of this type. In dementia paralytica, as indicated in a previous paper, we have found the procedure of value in prognosis, and it has given us much information as to the mechanism of the treatment by malaria.

We think that the procedure may be of value in treating mental deficiency. In many cases an increased pressure of the spinal fluid is noted, with an atrophic pattern, which in some cases may be due to the increase of fluid pressure.

In most cases the method of choice is that without anesthesia, but we see no contraindications to the use of ether. Carpenter's report of its use is encouraging.

SUMMARY AND CONCLUSIONS

Encephalography, as a new method of precision in diagnosis, is of great value. With care it is possible to interpret the roentgen findings in terms of anatomy, and we have attempted to establish this by a few comparisons. We believe that this procedure will add much to an understanding of the pathologic changes in the brain.

BIBLIOGRAPHY

Abramowitsch, D., and Winkler, H.: Messungen im Stereoencephalogramm, Ztschr. f. d. ges. Neurol. u. Psychiat. **127**:454, 1930.

Bingel, A.: Die röntgenographische Darstellung des Gehirns, Klin. Wchnschr. **1**:2191, 1922.

Buchanan, A. L.: Experiences with Encephalography, M. J. Australia **2**:812, 1929.

Carpenter, E. R.: Encephalography: Lumbar Puncture and Trephine Methods, Am. J. M. Sc. **173**:333, 1927.

Dandy, W. E.: Ventriculography Following the Injection of Air into the Cerebral Ventricles, Am. J. Roentgenol. **6**:26, 1919.

Ebaugh, F. G.; Dixon, H. H.; Kiene, H. E., and Allen, K. D.: Encephalographic Studies in General Paresis, Am. J. Psychiat. **10**:737 (March) 1931.

Farnell, F. J.; Howes, S. F. H., and Hudson, J. B.: Studies in Pneumoencephalography, Rhode Island M.J. **13**:115 (Aug.) 1930.

Friedman: Experiences with Encephalography Via the Lumbar Route, Bull. New York Acad. Med. **4**:503, 1928.

Kauffmann, Hellmuth: Die Technik der Enzephalographie und Ventriculographie und das normale Enzephalogramm, Beitr. z. klin. Chir. **136**:649, 1926.

Martin, C. L., and Uhler, Claude: Roentgenography of Intracranial Passages Following Spinal Air Injection, Am. J. Roentgenol. **9**:543, 1922.

Meyer, Ernst: Encephalographische Befunde aus neurologischem und psychiatrischem Gebiete, Arch. f. Psychiat. **89**:177, 1930.

Pancoast, H. K., and Fay, Temple: Encephalography: Roentgenological and Clinical Considerations for Its Use, Am. J. Roentgenol. **21**:421 (May) 1929.

Pendergrass, E. P.: Indications and Contraindications of Encephalography and Ventriculography, J. A. M. A. **96**:408 (Feb. 7) 1931.

Interpretation of Encephalographic Observations, Arch. Neurol. & Psychiat. **23**:946 (May) 1930.

Penfield, W. G.: Cerebral Pneumography: Its Dangers and Uses, Arch. Neurol. & Psychiat. **13**:580 (May) 1925.

Rosenheck, Charles: Encephalography: The Development of Hemiplegia Following Its Use, With Report of a Case, Arch. Neurol. & Psychiat. **22**:575 (Sept.) 1929.

Schreiber, Frederic: Equipment for Encephalography, Am. J. Roentgenol. **23**:427, 1930.

Waggoner, R. W.: Encephalography, Am. J. M. Sc. **174**:459, 1927.

Woods, A. R.: Encephalography, U. S. Vet. Bur. M. Bull. **5**:26, 1929.

RELATION BETWEEN MYASTHENIA GRAVIS AND EXOPHTHALMIC GOITER

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Since Graves [1] and Basedow [2] first described the disease bearing their names and Wilks [3] and Erb [4] first described cases of myasthenia gravis under the captions of bulbar paralysis and bulbar symptom complex, several descriptions of cases presenting the signs and symptoms of both these diseases have appeared in the literature. Such a remarkable group of cases with the symptoms and signs of these apparently distinct diseases warrants an analysis with a view toward determining whether or not any definite relationship exists. It is thought that any case of this kind should be reported, with such comments and conclusions as may be justified toward establishing or negating any such relationship.

REPORT OF A CASE

History.—A married Jewish housewife, 49 years of age, was first seen by Dr. S. G. Schenck in April, 1929. For one year she had complained of nervousness and profuse perspiration, and for several months there were pain in the upper abdominal region and anorexia. Physical examination at that time showed moderate exophthalmos, tremor of the tongue and hands, a palpable thyroid gland, a marked von Graefe sign, a rapid pulse and dark pigmented skin. The basal metabolic rate was plus 50 per cent. A diagnosis of exophthalmic goiter was made, and roentgen therapy to the thyroid gland was instituted. On reexamination, in January, 1930, the patient presented a normal pulse rate, marked recession of the ocular signs and disappearance of the tremor. Subjectively, she then felt much improved, despite the basal metabolic rate of plus 32 per cent.

In September, 1930, the patient again came under observation, complaining of marked weakness, drooping of the eyelids and diplopia, all having appeared suddenly two weeks before. Hoarseness was present for one week. Examination at

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From the medical service of Dr. M. A. Rabinowitz, Jewish Hospital, Brooklyn.

1. Graves, Robert J.: Clinical Lectures on the Practice of Medicine, M. & S. J., lecture 12, series 1, 1838, p. 134.

2. von Basedow: Exophthalmus durch Hypertrophie des Zellgewebes in der Augenhöhle, Wchnschr. f. d. ges. Heilk. **6**:197 (March 28) 1840.

3. Wilks, S.: Bulbar Paralysis, Fatal, No Disease Found, Guy's Hosp. Rep. **22**:54, 1877.

4. Erb, W.: Ueber einen neuen, wahrscheinlich bulbären Symptomkomplex, Arch. f. Psychiat. **9**:336, 1878.

this time revealed ptosis of the left upper lid, limitation of motion of both eyeballs in all directions, tremor of the hands and marked loss of power in the extremities. The patient was then admitted to the hospital.

Examination.—She was found to be well oriented and cooperative, lying quietly in bed, with the mouth half open, and the face expressionless. There were: marked ptosis of the left upper lid, complete upper left ophthalmoplegia externa and moderate ptosis of the right eyelid, the right eyeball moving incompletely in lateral directions. The pupils were equal and reacted well to light and in accommodation. The fundi were normal. The thyroid gland was not enlarged, and the pulse rate was not rapid. The patient exhibited marked generalized muscular weakness, so that she could not sit up without aid and could not stand unsupported.

Appearance of patient when admitted to the hospital.

Her phonation had a nasal character and the voice became weak and indistinct after pronouncing a few words. There was considerable difficulty in swallowing.

Examination of the blood showed: hemoglobin, 75 per cent (Dare); erythrocytes, 4,990,000, and leukocytes, 4,650, of which polymorphonuclears constituted 59 per cent, lymphocytes, 39 per cent and monocytes, 2 per cent. The Wassermann and Kahn reactions of the blood were negative; the blood sugar during fasting was 133 mg. per hundred cubic centimeters of blood; the spinal fluid was normal, and the basal metabolic rate was plus 48 per cent. A roentgenogram of the chest did not reveal a substernal thyroid gland or a thymic shadow. An electrocardiogram indicated some myocardial involvement. The myasthenic reaction was positive.

Course.—The patient would feel distinctly better and stronger during the morning hours. The ocular movements were better, the speech was more distinct, and there was more power in the extremities. Later in the day, the patient's move-

ments were slower and her strength failed. Very significant was the effect of ephedrine sulphate. When the drug was administered in doses of 0.1 Gm. three times a day, the patient felt more cheerful, the ptosis improved, the movements of the eye became more marked, and there was noticeable improvement in phonation and deglutition. On discontinuing the ephedrine the patient soon lapsed into her former state, and when the drug was readministered she would again improve. She left the hospital after remaining there for eight weeks and died at home suddenly a few weeks later. During the last few weeks of illness, for reasons beyond our control, the ephedrine had been discontinued and compound solution of iodine was given instead. A postmortem examination was not obtained.

Comment—The case presented is that of a patient in whom symptoms and signs of myasthenia gravis developed while she was suffering from exophthalmic goiter. It is significant that, although the basal metabolic rate was highly elevated (plus 48 per cent), the usual signs of exophthalmic goiter, such as tachycardia, exophthalmos, von Graefe sign and struma, were absent. The entire picture was now overshadowed by the signs of myasthenia gravis. An important observation is the marked improvement and relief that the patient obtained from the administration of ephedrine. We were led to institute this mode of therapy because of the experience of Edgeworth,[5] who herself obtained such relief from myasthenia gravis by taking ephedrine that she was able to pursue her work with comfort, and the information given to us by Dr. M. A. Rabinowitz that a patient of his with myasthenia gravis was able to return to his professional duties as a pharmacist while taking ephedrine.

REVIEW OF REPORTED CASES OF MYASTHENIA GRAVIS ASSOCIATED WITH EXOPHTHALMIC GOITER

WARNER.[6]—Double external ophthalmoplegia with bilateral weakness of the muscles of the face developed in a woman, aged 25, who had had exophthalmic goiter for four years.

BRISTOWE.[7]—Three years later, the patient whose case was reported by Warner presented diplopia, ptosis of both lids, double external squint and incomplete paralysis of the external ocular muscles. On postmortem examination, no abnormalities were found in the brain or spinal cord.

FÉREOL.[8]—Diplopia and paresis of the external ocular muscles developed in a man (age not given) with exophthalmic goiter.

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5. Edgeworth, H.: A Report of Progress on the Use of Ephedrine in a Case of Myasthenia Gravis, J. A. M. A. **94**:1136 (April 12) 1930.

6. Warner, F.: Ophthalmoplegia Externa Complicating Graves' Disease, M. Times & Gaz. **2**:541, 1882.

7. Bristowe, John S.: Cases of Ophthalmoplegia Complicated with Various Other Affections of the Nervous System, Brain **8**:313, 1885-1886.

8. Féreol, M.: Report of a Case Before the Société médicale des hôpitaux, Gaz. hebd. de méd. **26**:112, 1889.

FINLAYSON.[9]—A woman, aged 37, had exophthalmic goiter with drooping of the eyelids, diplopia and ophthalmoplegia.

MAUDE.[10]—A woman, aged 47, had had a goiter for nineteen years before ptosis of the lids and facial paralysis developed.

VOSS.[11]—A woman, aged 22, had a large thyroid gland, exophthalmos and generalized weakness. She also presented diplopia, right facial paralysis and weakness of the external ocular muscles.

POSEY.[12]—A woman, aged 43, had exophthalmos, palpitation and nervousness. Later, ophthalmoplegia and difficulty in drawing up the corner of the mouth developed. Posey cited cases that were reported by Ballet, Liebrecht, Buschan, Mannheim, Mobius and Jendrassik, in which the patient exhibited extra-ocular muscular palsy and exophthalmic goiter.

MEYERSTEIN.[13]—A woman, aged 33, had a goiter for twenty years. Ptosis, complete left external ophthalmoplegia and paresis of the right side of the body then suddenly developed. She also had a large thyroid gland and exophthalmos. The symptoms were always less in the morning than later in the day.

RENNIE.[14]—A man, aged 27, had exophthalmic goiter and myasthenia gravis. This patient was seen eleven years later, when he had only residual signs of goiter and paresis of the external ocular muscles. The graver myasthenic symptoms had improved.

RENNIE.[15]—A woman, aged 30, had an enlarged thyroid gland, exophthalmos, complete external ophthalmoplegia, regurgitation of food through the nose and weakness of the muscles of the head and neck.

KAPPIS.[16]—A woman, aged 20, had had a goiter since the age of 9 years, which had gradually increased in size. She presented exophthalmos and ptosis of both lids; the eyeballs moved but slightly in all directions, and at times there was complete ophthalmoplegia.

BERNHARDT.[17]—A woman, aged 22, had exophthalmos, ptosis of the left upper lid and external ophthalmoplegia. A few months later, ptosis of the right eyelid set in.

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9. Finlayson, J.: On the Paralysis of the Third Nerve as a Complication of Graves' Disease, Brain **13**:383, 1890.

10. Maude, A.: A Case of Ophthalmoplegia with Graves' Disease, Brain **15**: 121, 1892.

11. Voss, G.: Zur Symptomatologie und Therapie der Basedowschen Krankheit, Deutsche med. Wchnschr. **29**:590 (Aug. 13) 1903.

12. Posey, W. C.: Palsy of the Extraocular Muscles in Exophthalmic Goiter, Am. J. M. Sc. **128**:66 (July) 1904.

13. Meyerstein, R.: Ueber das kombinierte Vorkommen von Myasthenie und Basedow'scher Krankheit, Neurol. Centralbl. **23**:1089, 1904.

14. Rennie, G. E.: Exophthalmic Goiter Combined with Myasthenia Gravis, Rev. Neurol. & Psychiat. **6**:229, 1908; Exophthalmic Goiter Combined with Myasthenia Gravis, M. J. Australia **1**:416 (Nov. 15) 1919.

15. Rennie, G. E.: Myasthenia Gravis with Exophthalmic Goiter, Rev. Neurol. & Psychiat. **11**:475 (Sept.) 1913.

16. Kappis, M.: Ueber Gehirnnervenlähmungen bei der Basedowschen Krankheit, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **22**:657, 1910-1911.

17. Bernhardt, M.: Basedowsche Krankheit und Augenmuskullähmung, Neurol. Centralbl. **30**:706 (July) 1911.

McKendree.[18]—A woman (age not given) had the facies and exophthalmos of exophthalmic goiter. Ptosis, diplopia, ophthalmoplegia, generalized muscular weakness and weakness on phonation, deglution and mastication suddenly developed.

Heuer.[19]—A man, aged 23, had had a goiter and symptoms of exophthalmic goiter. One year later, ptosis, diplopia, involvement of the muscles of mastication and weakness of the extremities developed.

den Boer.[20]—In this case there developed ptosis and external ophthalmoplegia ten years after the onset of exophthalmic goiter.

Jackson and Bates.[21]—A man, aged 26, had exophthalmos with weakness of the ocular muscles, weakness of the muscles of deglutition and indistinct phonation.

Vedsmand.[22]—In this case there was exophthalmic goiter with signs and symptoms of myasthenia gravis.

Jaensch.[23]—A woman, aged 37, had exophthalmos, diplopia and external ophthalmoplegia.

Dudgeon and Urquhart.[24]—These authors cited a case of exophthalmic goiter with myasthenia gravis.

Burger.[25]—A woman, aged 51, had thyrotoxicosis for two years, with marked weakness in the extremities so that she could not get up without aid. She also had difficulty in swallowing and indistinct phonation. All these symptoms improved later.

Wolff, Keutmann and Cobb.[26]—A man, aged 30, had a large thyroid gland, exophthalmos and a basal metabolic rate of plus 55 per cent. Thyroidectomy was performed. A short while later, rapidly progressing muscular weakness, difficulty in swallowing, weakness in phonation and ophthalmoplegia externa developed.

Wedd and Permar.[27]—A woman, aged 37, had had a partial thyroidectomy twelve years previously for exophthalmic goiter. Diplopia, fatigue, general muscular weakness and ophthalmoplegia externa suddenly developed. She was able

18. McKendree, Charles A.: A Case of Myasthenia Gravis, J. A. M. A. **63**: 1553 (Oct. 31) 1914.

19. Heuer, George J.: The Cerebral Nerve Disturbances in Exophthalmic Goiter, Am. J. M. Sc. **151**:339 (March) 1916.

20. den Boer, M.: Een geval van Struma met Ophthalmoplegia Quassi Totalis Externa, Nederl. tijdschr. v. geneesk. **64**:2284 (June 19) 1920.

21. Jackson, A. S., and Bates, A. D.: Myasthenia Gravis: Report of a Case, J. A. M. A. **81**:114 (July 14) 1923.

22. Vedsmand, H.: Myasthenia gravis, Morbus Basedowii (pluriglandular insufficiens?), Ugesk. f. læger **85**:405 (June 7) 1923.

23. Jaensch, P. A.: Augenmuskellähmungen bei Basedowscher Krankheit, Deutsche med. Wchnschr. **50**:1249 (Sept. 12) 1924.

24. Dudgeon, L. S., and Urquhart, A. L.: Lymphorrages in the Muscles in Exophthalmic Goiter, Brain **49**:182 (June) 1926; personal communication.

25. Burger, W.: Ueber Thyrotoxikose mit spinalen Symptomen, Deutsches Arch. f. klin. Med. **162**:355 (Dec.) 1928.

26. Wolff, H. G.; Keutmann, H., and Cobb, S.: The Electromyogram in Myasthenia Gravis, Brain **51**:508 (Dec.) 1928.

27. Wedd, M. A., and Permar, H. H.: Ophthalmoplegia in Graves' Disease, Am. J. M. Sc. **175**:733 (June) 1928.

to move her eyes in the morning, while later in the day the movements became weaker. Postmortem examination showed no evidence of a cranial lesion.

STERLING.[28]—A woman, aged 36, presented, besides a large thyroid gland and moderate exophthalmos, marked weakness of the extremities, marked fatigability of the trunk and neck muscles, and difficulty in phonation, mastication and deglutition.

GARVEY.[29]—A man, aged 40, had ptosis of the lids, diplopia, bilateral external ophthalmoplegia and weakness. He also had signs and symptoms of exophthalmic goiter.

COMMENT

Neither of the diseases under consideration, when occurring alone, shows lesions of the central nervous system or of the spinal cord. Two of the cases of the group reviewed (Bristowe[7] and Wedd and Permar[27]) came to necropsy, and no lesions were demonstrated in the central nervous system. Wolf, Keutmann and Cobb[26] were able to show that in myasthenia gravis the defect lies peripheral to the anterior horn cells, and that there is no alteration in the nerve. One of the cases they studied in this manner was one of a combination of myasthenia gravis with exophthalmic goiter.

Few cases of myasthenia gravis show evidence of exophthalmic goiter, but the majority of cases of exophthalmic goiter show evidence of myasthenia to a greater or lesser degree. Plummer gave diagnostic significance to the sign of weakness of the quadriceps muscle group, and differentiated between the weakness of these muscles in hyperthyroidism and the lassitude and mental fatigue in the psychoneurotic patient. Lahey[30] described a similar sign. The element of muscular exhaustion and weakness is also brought out in some of the ocular signs found in the hyperthyroid state. The Möbius sign really denotes weakness of the rectus muscles. Sucker[31] described a relevant sign in exophthalmic goiter: When the eyes are fixed laterally on an object, and the object is suddenly swung to the midline, one of the eyes fails to follow the other, and an apparent divergent strabismus thus becomes manifest. The author explained this sign as due to muscular exhaustion.

In the pathology and pathogenesis of these two diseases there are several factors common to both which suggest a relationship between them, although a common factor cannot as yet be designated.

28. Sterling, W.: Maladie de Basedow, myasthénie et amyotrophie progressive, Rev. neurol. **1**:93 (Jan.) 1930.

29. Garvey, J. L.: Ophthalmoplegia and Graves' Disease, Ann. Int. Med. **3**:917 (March) 1930.

30. Lahey, F. H.: Quadriceps Test for Myasthenia in Thyroidism, J. A. M. A. **87**:754 (Sept. 4) 1926.

31. Sucker, G. F.: A New Ocular Muscle Symptom in Exophthalmic Goiter, J. A. M. A. **68**:1255 (April 28) 1917.

Thus, in exophthalmic goiter one finds the following: 1. There is a marked hyperplasia of the lymphatic tissues, viz., the thymus, the spleen and the regional lymph nodes.[32] 2. The suprarenal glands are usually small.[32a] 3. Lymphorrhages of the same type as those found in myasthenia gravis have been found in muscle tissue in cases of exophthalmic goiter by Dudgeon and Urquhart.[34] 4. Lymphocytosis is a prominent finding in exophthalmic goiter. 5. The occasional occurrence of glycosuria and lowered carbohydrate tolerance in exophthalmic goiter are well known. Creatinuria, which is absent in normal adults, occurs in this disease.[33] Palmer, Carson and Sloan [34] showed that the creatine disappeared when improvement followed the administration of iodine.

In myasthenia gravis the following are found: 1. There is a hyperplasia of the lymphatic tissues.[35] 2. The suprarenal glands are involved. Mandlebaum and Celler [36] have demonstrated lymphorrhages in the suprarenal cortex. 3. The prominent feature of myasthenia gravis is the finding of lymphorrhages in muscles, which was fully described by Buzzard.[37] 4. Lymphocytosis is present with either a normal white cell count or a slight leukocytosis.[35] 5. Williams and Dyke [38] showed that there is a definite lowering of carbohydrate tolerance. They also demonstrated that creatine is present in the urine on a diet free from creatine and creatinine.

CONCLUSION

From a consideration of the pathologic findings, the involvement of interrelated endocrine glands and the similarity in the metabolic disturb-

32. (*a*) Marine, D.: Remarks on the Pathogenesis of Graves' Disease, Am. J. M. Sc. **180**:767 (Dec.) 1930. (*b*) Haberer, H.: Thymusreduktion und ihre Erfolge, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **27**:199, 1913-1914. (*c*) Moschcowitz, E.: The Nature of Graves' Disease, Arch. Int. Med. **46**:610 (Oct.) 1930. (*d*) Seelig, M. G.: The Rôle of the Thymus in Exophthalmic Goiter, Interstate M. J. **20**:678 (July) 1913. (*e*) Margolis, H. M.: The Possible Significance of the Thymus Gland in the Syndrome of Hyperthyroidism, Ann. Int. Med. **4**:1112 (March) 1931. (*f*) Boit, H.: Ueber die Komplikation des Morbus Basedowii durch Status lymphaticus, Frankfurt. Ztschr. f. Path. **1**:187, 1907.

33. Shaffer, P.: The Excretion of Creatinin and Creatin in Health and Disease, Am. J. Physiol. **23**:1 (Oct.) 1908.

34. Palmer, W. W.; Carson, D. A., and Sloan, L. W.: The Influence of Iodin on the Excretion of Creatin in Exophthalmic Goiter, J. Clin. Investigation **6**:597 (Feb. 20) 1929.

35. Keschner, M., and Strauss, I.: Myasthenia Gravis, Arch. Neurol. & Psychiat. **17**:337 (March) 1927.

36. Mandlebaum, F. S., and Celler, H. L.: A Contribution to the Pathology of Myasthenia Gravis, J. Exper. Med. **10**:308 (April) 1908.

37. Buzzard, E. F.: The Clinical History and Post-Mortem Examination of Five Cases of Myasthenia Gravis, Brain **28**:438, 1905.

38. Williams, B. W., and Dyke, S. C.: Observations on Creatinuria and Glycosuria in Myasthenia Gravis, Quart. J. Med. **15**:269 (July) 1922.

ances, one is led to conclude that the two diseases, viz., myasthenia gravis and exophthalmic goiter, are distinctly related and that this accounts for their not infrequent simultaneous occurrence.

SUMMARY

1. A case of exophthalmic goiter with myasthenia gravis is reported.

2. The heretofore reported cases of exophthalmic goiter with myasthenia gravis are reviewed.

3. The cases of the combination of myasthenia gravis with exophthalmic goiter do not exhibit lesions of the brain or of the spinal cord.

4. There is a similarity in the pathology, pathogenesis and endocrine dysfunction in exophthalmic goiter and myasthenia gravis.

5. Attention is called to the beneficial effect of ephedrine in myasthenia gravis alone, as well as when it is complicated by exophthalmic goiter.

OXYGEN CONSUMPTION ("BASAL METABOLIC RATE") IN SCHIZOPHRENIA

II. DISTRIBUTIONS IN TWO HUNDRED AND FOURTEEN CASES

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WITH THE TECHNICAL ASSISTANCE OF ANNA WALSH, R.N.
BOSTON

The fact that the incidence of schizophrenia correlates with both constitutional and genetic factors implies that the organic elements in the picture are of primary significance.[1] This follows irrespective of the weight that one may attach to psychogenic factors. The psychosis is characterized by numerous deviations from physiologic normality. It would seem desirable, therefore, that the disorder be described in its organic aspects fully and accurately. In standard textbooks of psychiatry the conventional neglect of the organic in favor of the psychologic is striking. This is the more remarkable in that the organic features lend themselves much more readily than do the mental to accurate description. While it is true that "mere enumeration" of traits is a methodology of strictly limited significance, attempts to advance in research without an adequate description of the phenomena under study are likely to be characterized by ineptitudes.

One of the purposes of our own investigation is to assemble the data for an accurate description of a representative group of subjects. For this purpose a statement of both the "central tendencies" and the "dispersion" of a wide variety of characteristics is desirable. In previous publications evidence has been submitted regarding galactose tolerance,[2] the "basal metabolic rate"[3] and the blood pressure.[4] Reports on various other features are in preparation.

In our first report,[3] the literature on basal metabolism in schizophrenia up to 1928 was reviewed. Records were found of 206 cases.

With the collaboration of the Research Staff of the Worcester State Hospital.

From the Worcester State Hospital and the Memorial Foundation for Neuro-Endocrine Research.

1. Hoskins, R. G.: An Analysis of the Schizophrenia Problem from the Standpoint of the Investigator, J. A. M. A. **97**:682 (Sept. 5) 1931.

2. Sleeper, F. H., and Hoskins, R. G.: Galactose Tolerance in Dementia Praecox, Arch. Neurol. & Psychiat. **24**:550 (Sept.) 1930.

3. Hoskins, R. G., and Sleeper, F. H.: Basal Metabolism in Schizophrenia, Arch. Neurol. & Psychiat. **21**:887 (April) 1929.

4. Freeman, H.; Hoskins, R. G., and Sleeper, F. H.: The Blood Pressure in Schizophrenia, Arch. Neurol. & Psychiat. **27**:333 (Feb.) 1932.

To these were added 80 cases personally studied, making a total of 286. In the consolidated series, 15 subjects were reported as having basal metabolic rates above the conventional upper limit of normality, 134 within normal limits and 137 below normal. The mean rate in our series was 89.1 per cent of normal.[5] Fifty-six per cent of the rates fell below the level of 90 per cent, which was accepted as the lower level of normality. It was recognized that in our series, as well as in those of other investigators, the rates reported were undoubtedly well above the actual basal rates because of the difficulty in securing satisfactory test conditions.[6]

In 1927 and 1928, Fischer[7] published the findings on 39 additional subjects, 9 of whom, however, were in an early phase of the disorder and had normal rates. In the 30 well developed cases, in hebephrenic, catatonic and paranoid subjects, the range in the rate of oxygen consumption was from 67 to 93 per cent of normal, falling below 85 per cent in 8 cases, the average of the 30 cases being 86.4 per cent. Two thirds of the subjects showed a rate of 90 per cent or lower. In a series of 15 control cases of "depressive psychosis" the range was from 94 to 103 per cent, i. e., normal. In a series of arrested (*abgeklungene*) cases the range (omitting meaningless fractions) was from 82 to 101 per cent, and in a series of 8 cases showing recovery without bodily or psychic residual disturbances the range was from 95 to 103 per cent.

Appel and Farr[8] reported the basal rates of five schizophrenic patients who showed a normal range.

Henry[9] reported on 70 cases made up of paranoid, catatonic, hebephrenic and simple types of schizophrenia, together with 222 cases of psychoneuroses, psychopathic personality and other psychoses. He further subdivided his subjects in accordance with the emotional states.

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5. It seems preferable to express measurements in terms of percentage of normal rather than conform to the awkward convention of using plus and minus signs. Thus, "90 per cent," as the term is used herein, is the equivalent of "— 10 per cent."

6. "Basal metabolism is an expression of the heat production of the body in complete mental and physical repose, and in the postabsorptive state" (Hawk, P. B., and Bergheim, O.: Practical Physiological Chemistry, ed. 10, Philadelphia, P. Blakiston's Son & Co., 1931). Basal metabolism measures "the heat that is produced during the liberation of energy that is sufficient only to maintain the automatic functions of the body" (King, J. T., Jr.: Basal Metabolism, Baltimore, Williams & Wilkins Company, 1924).

7. Fischer, S.: Gasstoffwechselveränderungen bei Schizophrenen (I. Mitteilung): Differentialdiagnostische Bedeutung, Klin. Wchnschr. **6**:1987, 1927; Gasstoffwechselveränderungen bei Schizophrenen, Arch. f. Psychiat. **83**:205, 1928.

8. Appel, K. E., and Farr, C. B.: The Specific Dynamic Action of Protein in Relation to Mental Disease, J. Nerv. & Ment. Dis. **70**:43 (July) 1929.

9. Henry, G. W.: Basal Metabolism and Emotional States, J. Nerv. & Ment. Dis. **70**:598 (Dec.) 1929.

Among the schizophrenic patients the average rate of oxygen consumption of the depressed, underactive, undertalkative group was 89 per cent; of the apathetic group, from 92 to 94 per cent, and of the apprehensive, tense, agitated group, from 104 to 111 per cent of normal. The ranges in the other psychoses were not significantly different from those in schizophrenia. Although he stated that standard criteria for basality were met, both the range of deviations noted and the inclusion of tense, agitated patients would indicate that a considerable proportion of the subjects were not actually in a basal state. Henry's figures are in contrast with those of Fischer, who found that the rates of oxygen consumption in the "depressive psychosis" lay within the normal range, whereas in schizophrenia marked reduction was noted.

Claude, Baruk and Médakovitch [10] reported the results of repeated tests on 16 schizophrenic subjects, either catatonic or hebephrenic-catatonic. A wide range was noted. That of the total series was from 43 to 149 per cent of normal. The greatest difference noted in any single case was 81 points between the lowest and highest readings. The lowest reading obtained in each case ranged from 43 to 92 per cent of normal. All but 2 of the 16 patients gave at least one reading below 85 per cent.

THE PRESENT STUDY

Methods.—The study here reported was made on 214 patients, including 80 previously reported. Standard methods of making determinations of oxygen consumption were employed throughout. The patients were brought to the laboratory in the early morning, before breakfast, and were kept quietly recumbent on a couch for at least half an hour before the test. The determinations were all made by one of us (Miss Walsh) or under her general supervision. The Benedict closed-circuit apparatus was used. A comfortable nose-clip with sponge-rubber pads closed the nostrils, and the connection with the apparatus was made by means of a rubber mouthpiece. The necessity for special care with psychotic patients to avoid leakage around the mouthpiece was respected. The apparatus was frequently inspected, and more recently was tested daily for leaks. Care was taken to avoid the use of spent soda lime. Careful observations were continued throughout the rest and the test periods. If the patients showed other than minor activity before the tests or overt evidence of tension, such as restlessness or talking during the tests, the results were discarded and the examinations repeated. Commonly, 2 consecutive tests were made on each patient. The lower of the 2 determinations on any given day, technical errors having been excluded, was selected as the more representative. The findings were calculated to the Aub-Dubois and the Harris-Benedict standards, and the average of the 2 results taken as characteristic. In the cases in which but a single technically "satisfactory" test was secured, it was taken as representative.

Since many of the determinations were made primarily for diagnostic purposes, the term "satisfactory" was less rigorously interpreted

10. Claude, H.; Baruk, H., and Médakovitch, G.: Le métabolisme basal dans la catatonie et l'hébéphréno-catatonie, Encéphale **23**:797, 1928.

than would be the case were one concerned solely with scientific exactitude. Thus it happens that in a considerable number of cases only approximate relaxation was secured. Accordingly, the values herein reported ranged unquestionably above the true basal rates.

Composition of the Group.—The aim of our study, so far as descriptive features are concerned, has been to assemble a group of male patients representative of the hospital at large. Chart 1 shows the composition of the group as regards age. The average age was 30.2 years, though the largest number of cases (54) fell in the 25 to 30 year group. There was only 1 subject younger than 15 years and only 5 older than 50 years. The "standard deviation" of 8.4 years measures conventionally the variation within the group, the rates in two thirds of the cases falling within 8.4 years of the average or within the range of 21.8 and 38.6 years. In view of the fact that state mental hospitals

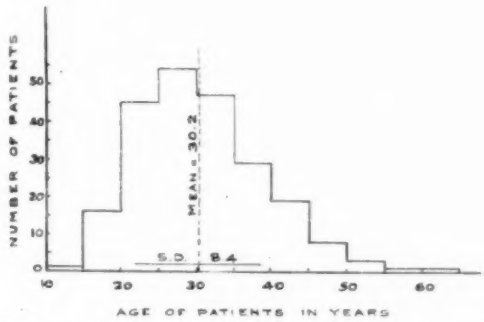

Fig. 1.—Distribution graph showing composition of group as to age.

inevitably accumulate a large proportion of chronic cases, our research group is probably therefore not entirely representative. It includes proportionately an excessive number of subjects in the earlier phases of the disorder. In a later publication it is proposed to consider the influence of age as such.

Chart 2 shows the composition of the group as regards the period of hospitalization at the beginning of the study. "On the average," the patients had been in the hospital 4.4 years. It will be observed that the shorter hospital periods greatly predominate, 99 of the patients falling within the "1 year group." Actually, the period varied in this group from a few days to an entire year. If the entire graph were constructed with "class intervals" of a month instead of 2 years we should obtain a typical skewed, "cocked-hat" distribution rather than the apparent "J-curve." The period of the investigation varied in individual cases from a few weeks to 2 or 3 years; hence if the data of conclusion of the study of each patient had been selected for graphing,

instead of the date of beginning, the whole distribution would have been shifted somewhat, though relatively not greatly, to the right. This curve brings out the special selection involved in our study. The average length of hospital stay of schizophrenic patients in Massachusetts state hospitals is 10.94 years.

Distribution of the Mean Rate for the Series as a Whole.—In chart 5 is shown the distribution of the total series, taking the average rate of oxygen consumption obtained in each patient. The mean value (average of the individual averages) was 88.3 per cent. The range was from 57 to 122 per cent, neglecting a single instance of 147 per cent. The largest single group (45 patients) fell in the 80 to 85 per cent range.

For statistical purposes the composition of the series is somewhat less than ideal. In a considerable proportion of the cases the mean

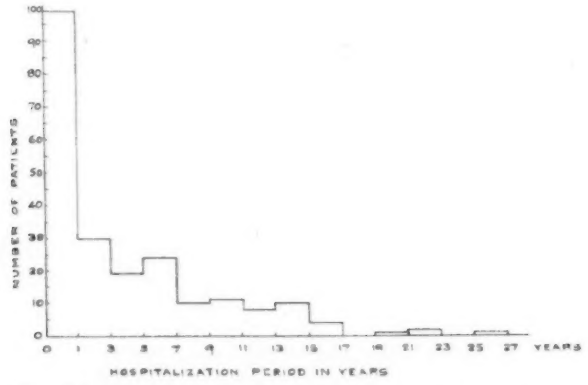

Fig. 2.—Distribution graph showing composition of group as to period of hospitalization at the beginning of the study.

oxygen consumption value was computed from 10 to 15 individual readings; the number gradually diminished as the periods of study decreased, and in 57 cases only a single test was available. From various tests of inner consistency, however, it appears that these 57 cases were so distributed as not significantly to distort the total picture; i. e., no systematic shift was introduced.

Many of the patients had been under endocrine or other drug treatment during their sojourn on the research service. Since this included thyroid medication in 107 of the cases, there is a possibility that the average rate of oxygen consumption for the entire series was displaced in an upward direction. This disturbing factor was minimized, however, if not entirely obviated, by the arbitrary exclusion of all tests made within 3 months of the conclusion of such treatment.

Variability of Rate in Individual Patients.—For the purpose of establishing a paradigm, account must be taken of the range of findings for the individual patient over a considerable period of time. Chart 3 sets forth our results as regards this feature. The average range in oxygen consumption in all the subjects in the group was 21.6 points, with a standard deviation of 14.8. The skewing of the curve to the left shows a preponderance of the lesser degrees of variability. At one extreme we had 2 patients showing a difference of 70 points between the highest and lowest readings obtained. This is less than the extreme difference of 81 points noted by Claude,[10] but probably represents some degree of experimental error. At the other extreme was a group of 17 patients showing a range of 5 points or less. About 17 per cent of the patients showed ranges above 30 points. The relative variability in the entire series was 68.4 per cent. It must be emphasized, however, that we were dealing here with "run of the mine" material that is not

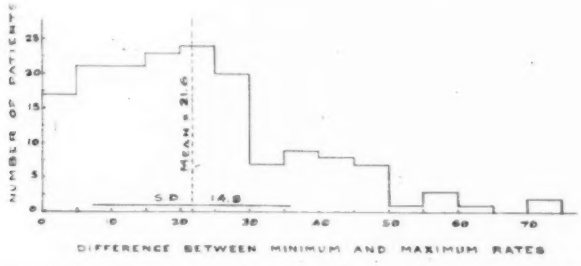

Fig. 3.—Distribution graph showing the difference between minimum and maximum rates of oxygen consumption observed in individual patients.

entirely representative as regards the point at issue. In some cases enough individual determinations were made to include the entire range over a period of months. But in the case of patients under study for short periods only 2 or 3 tests obtained within a few weeks were available. In 59 cases in the series only a single reading had been obtained. We are now accumulating a more homogeneous series of determinations that can be analyzed to present more accurately the range within a fixed period of time—in this case seven months. We hope ultimately also to present a distribution based on a longer standard interval of time.

The rate of oxygen consumption is of course determined by many variables, but for purposes of this discussion three factors are of particular importance. These are the technical errors of the method used, changes in the true basal rate coincident with changes in the clinical condition of the patient, and the degree of tension of the patient at any given time. With technical competence the errors of the method are negligible. One has to guard against only leakage in the calorimeter

system and the use of spent soda lime. Suffice it to say that particular care has been used to exclude such errors from the present study. The variations in the rate of oxygen consumption associated with changes in the clinical state of the patient will form the subject of a subsequent report.

As regards the variability in the individual patient in any given setting, our data are now fairly adequate in that we have on record hundreds of determinations of 2 or more consecutive readings under satisfactory test conditions. From this series 103 pairs of consecutive determinations were selected at random and the differences beween the readings were tabulated. In 50.5 per cent of the cases the first reading was the higher; in 46.5 per cent it was lower and in 3 per cent of the cases the rates were the same. The distribution is presented in chart 4.

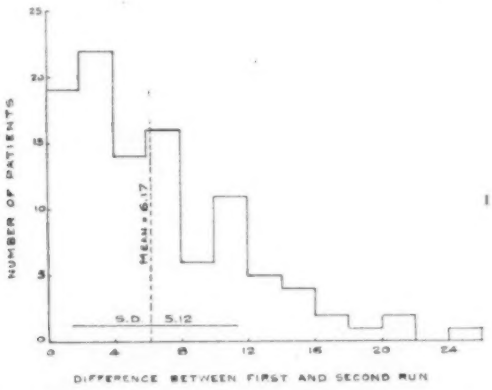

Fig. 4.—Distribution graph showing the difference between the first and second oxygen consumption rates obtained in consecutive determinations. This chart is based on 103 pairs of "satisfactory" readings selected at random (alphabetically).

The average difference in the oxygen consumption rate of this sample was 6.2 points, with a standard deviation of 5.1. In 53 per cent of the cases the difference between the consecutive tests was 5 points or less. In 32 per cent the difference lay between 6 and 11 points, while 14.6 per cent of the patients showed a difference of 12 or more points. The greatest single difference was 25 points. It will be recalled that we are dealing here with technically "satisfactory" determinations. Were tests included in which the patients gave evidences of intermittent tension, the differences would have been much greater.

Variability in the Series as a Whole.—Another method of studying the variability is to determine how far the average oxygen consumption rate of each patient departs from the lowest rate obtained in each. The average oxygen consumption rate of the entire series, as shown in

chart 5, was 88.3 per cent. This is closely similar to the average of 89.1 in our first series.[3] The rates of individual patients varied from 55 to 150 per cent. In two thirds of the cases, as shown by the standard deviation of 10.4, the rates fell within a range of 77.9 and 98.7 per cent. Expressed relatively, the coefficient of variation was 11.8 per cent. In data of this nature 11.8 per cent represents a relatively small scatter. When the *lowest readings* obtained on the individual patient were

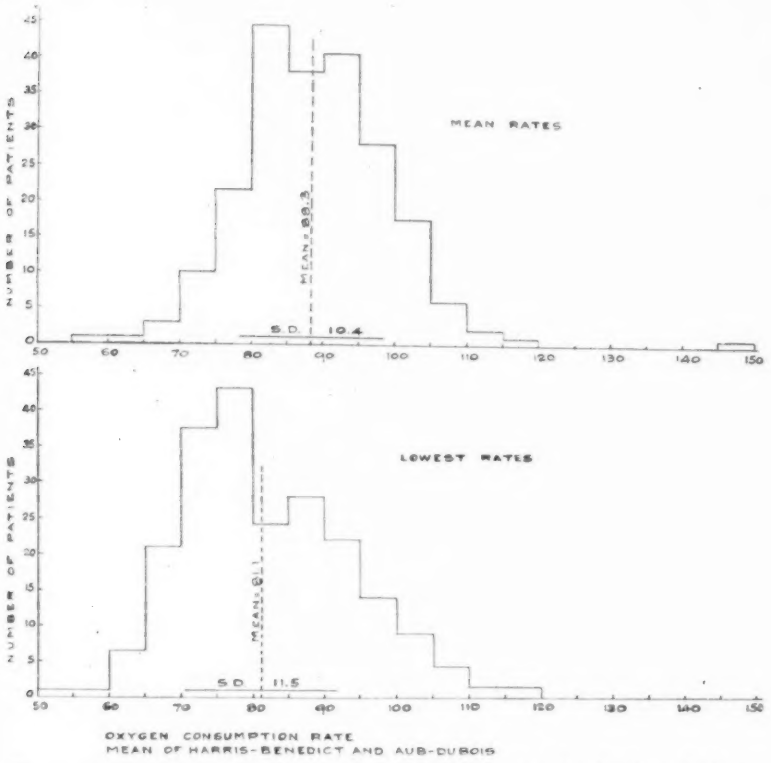

Fig. 5.—Comparative charts showing respectively the distribution of the mean and of the lowest rates of oxygen consumption obtained in each of 214 patients.

plotted, they were found to range from 50 to 120 per cent. However, only 7 per cent of the patients had rates above 100. In 76 per cent the rate fell below 89 per cent, and in half the series the lowest rate was below 80 per cent. Two thirds of the rates fell between 69.6 and 92.6 per cent. The mean was 81.1. The average lowest rate, then, for the series was 7.2 points less than the average mean rate of oxygen consumption.

Effect of Habituation.—In normal persons, repetitions of the test commonly result in a considerable degree of lowering of the basal rate.

Certainly, habituation to the test procedures renders it possible to secure better cooperation from almost all schizophrenic patients. The question suggests itself whether, after conventional quietude is secured, practice will result in further approach toward a true basal condition. Would the strain of keeping quiet actually introduce a compensatory degree of concealed tension? This problem lends itself to analytic investigation.

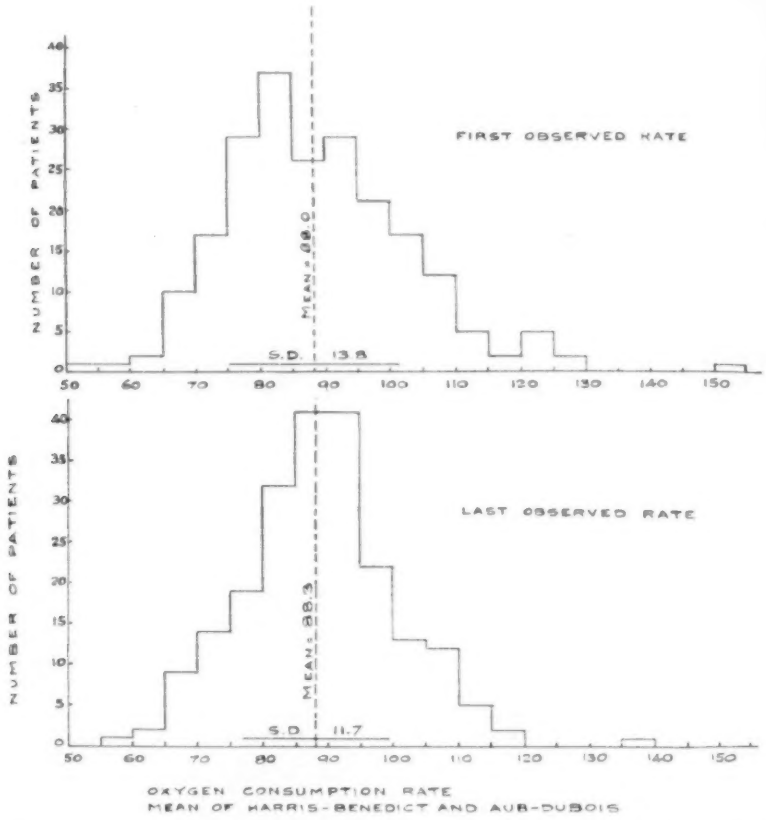

Fig. 6.—Comparative charts showing the difference, respectively, between the first and the last determinations of oxygen consumption rates in each of 214 patients.

A comparison of the first satisfactory determination with the last in a series of patients should throw light on the problem. In chart 6 is presented the results of such a comparison in 155 of the 214 cases in which two or more readings were available. In 59 cases a single observation only was made; hence the "first" and "last" readings are the same. The average first rate for the entire series of patients was 88.0 per cent, with a range from 50 to 150 points. The average last rate obtained

was 88.3 per cent, which is statistically equivalent to the average of the first readings, 88.0 per cent. In 67 of the individual cases the first reading was higher than the last by 5 or more per cent, and in 55 cases the last reading was the higher by an equal amount. In 33 cases there was essentially no difference. There is some degree of systematic error involved in this comparison, in that the earlier material was less rigorously selected than the later. Hence, the fact that the first and last readings show no difference is all the more striking.

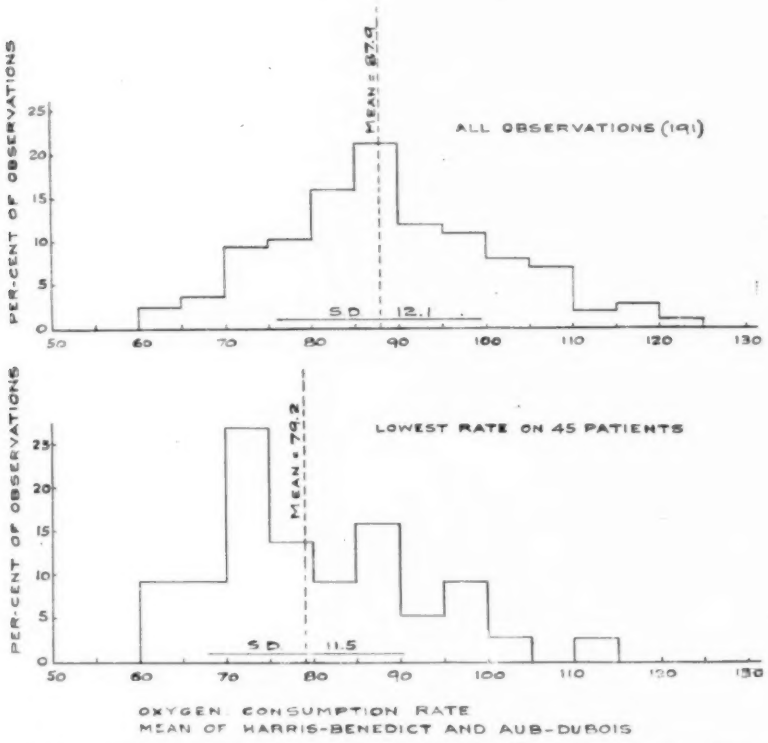

Fig. 7.—Graphs showing respectively the distribution of all determinations and of the lowest rate of oxygen consumption recorded in each of 45 catatonic patients.

Moreover, the modal values of the two curves suggest that the effect of habituation was actually to increase the rate of consumption. In any case it can be said of schizophrenic subjects that after a certain initial quietude is attained, further practice cannot be depended on to bring the patient closer to his real basal state.

Oxygen Consumption in Various Clinical "Types."—The question has often been raised whether the kraepelinian classification into subtypes represents any sort of genuine nosological grouping. If such were

the case, it might be anticipated that distinctive differences in the organic characteristics of the various types could be detected. Since the rate of oxygen consumption is a particularly meaningful indicator of the metabolic state of the patient, one might hope to find differences in this datum.

All the patients in our series were carefully studied as to anamnestic and presenting pictures, and were conventionally "typed." The group

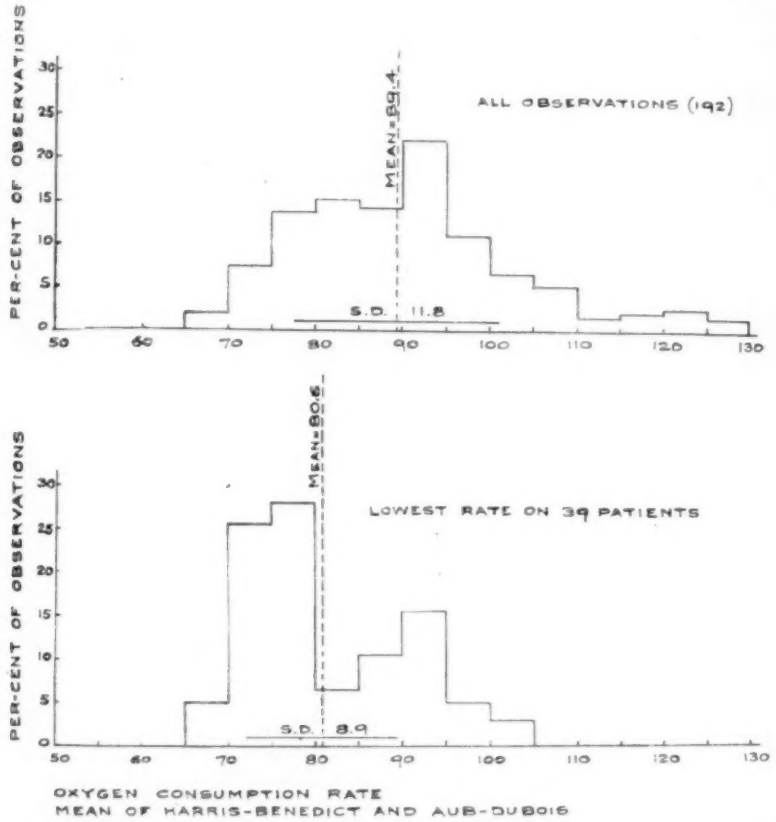

Fig. 8.—Graphs showing respectively the distribution of all determinations and of the lowest rate of oxygen consumption recorded in each of 39 hebephrenic patients.

diagnoses represent in each case the consensus of four or more trained psychiatrists. As is characteristic of schizophrenia, the clinical picture sometimes changed—and with it the diagnosis. The initial label, however, was kept throughout the study. Had there emerged any significant differences in oxygen consumption among the various groups, the material would have been reanalyzed with regard to change of label.

We had available determinations on 45 patients of the catatonic type, or 191 observations all told (chart 7). The average oxygen consumption for the group was 87.9 per cent of normal, with a standard deviation of 12.1. The average rate was therefore statistically identical in the catatonic and in the entire composite group, in which it was 88.3 per cent. The range in the catatonic group was from 62 to 120 per cent. It will be remembered that the selection of the lowest rate

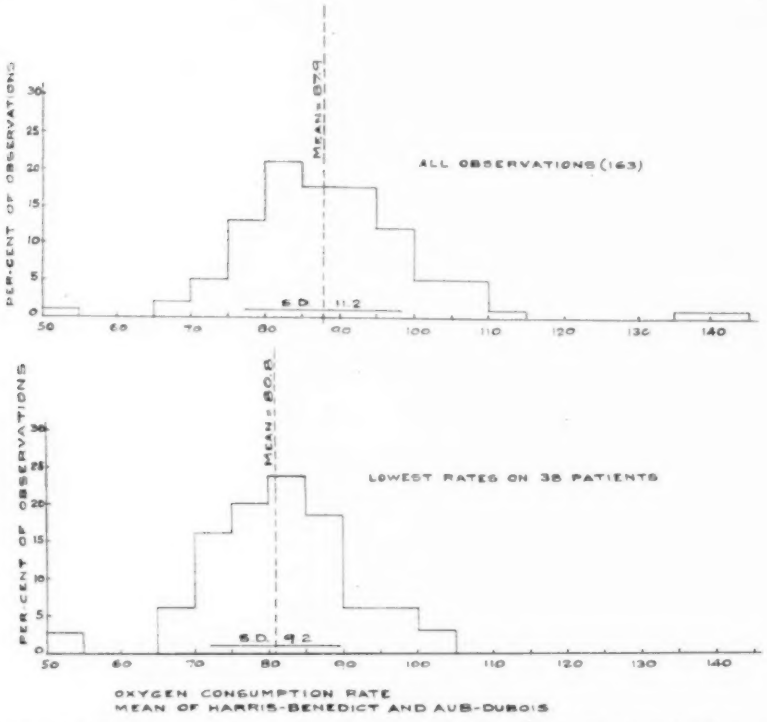
PER-CENT OF OBSERVATIONS
MEAN = 87.9
ALL OBSERVATIONS (163)
S.D. 11.2
50 60 70 80 90 100 110 120 130 140
PER CENT OF OBSERVATIONS
MEAN = 80.8
LOWEST RATES ON 38 PATIENTS
S.D. 9.2
50 60 70 80 90 100 110 120 130 140
OXYGEN CONSUMPTION RATE
MEAN OF HARRIS-BENEDICT AND AUB-DUBOIS

Fig. 9.—Graphs showing respectively the distribution of all determinations and of the lowest rate of oxygen consumption recorded in each of 38 paranoid patients.

as contrasted with the average rate for the composite series displaced the mean in a downward direction by 7.2 points. This fact can be used for a check of consistency in the subgroups. When the lowest individual reading obtained on each catatonic patient was graphed, the mean value was 79.2. This is 8.7 points below the mean of the average readings. The two sets of data, therefore, check satisfactorily in this regard.

In the hebephrenic group, 192 observations were available on 39 individual patients (chart 8). The mean for the entire series of obser-

vations was 89.4, and the whole distribution was rather similar to that in the catatonic group. The rate of 89.4 per cent is not significantly different from the rate of the composite group, 88.3 per cent. The lowest reading on each patient gave a distribution also similar to that of the lowest rate for the catatonic patients, the mean being 80.6. The difference between the mean of the "average" and of the "lowest" readings was 8.8, almost exactly the same as in the catatonic group.

In the paranoid group, the distributions of 163 observations on 38 patients gave curves again rather similar to those of the catatonic

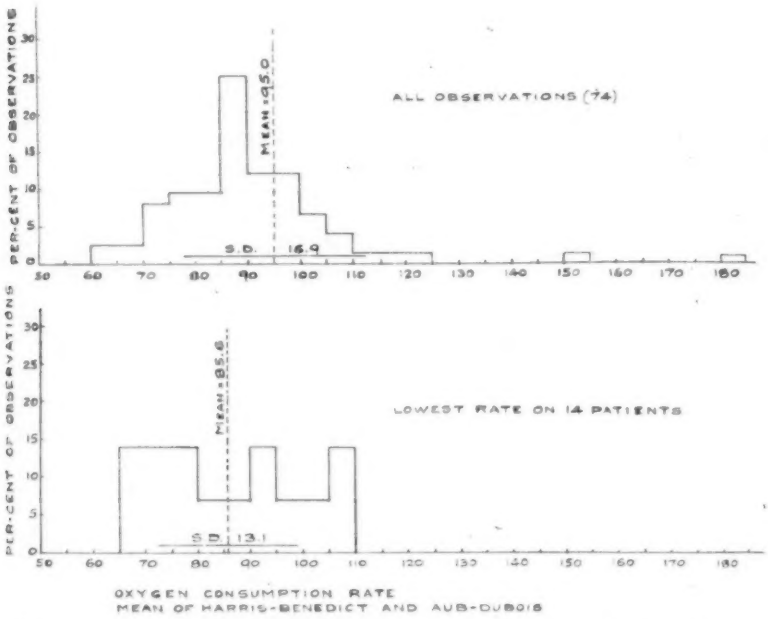
PER-CENT OF OBSERVATIONS
MEAN=95.0
ALL OBSERVATIONS (74)
S.D. 16.9
50 60 70 80 90 100 110 120 130 140 150 160 170 180
PER-CENT OF OBSERVATIONS
MEAN=85.6
LOWEST RATE ON 14 PATIENTS
S.D. 13.1
50 60 70 80 90 100 110 120 130 140 150 160 170 180
OXYGEN CONSUMPTION RATE
MEAN OF HARRIS-BENEDICT AND AUB-DUBOIS

Fig. 10.—Graphs showing respectively the distribution of all determinations and of the lowest rate of oxygen consumption recorded in each of 14 patients with schizophrenia of simple type.

group (chart 9). The mean of all observations was 87.9, and of the lowest individual rates, 80.8—a difference of 7.1.

In the "simple" type, only 74 observations on 14 patients were available (chart 10). These were distributed around a mean of 95.0 per cent for the average rate and of 85.6 per cent for the lowest rate in each case, a difference of 9.4. The observations suggest that the metabolic conditions in the "simple" variety approximate the normal more than do those of any other type.

We had available 358 observations on 78 patients in whom the characteristics were not sufficiently well defined to justify classification in

any of the conventional groups (chart 11). This series included a considerable number of patients with characteristics of two or three individual groups. The rates were distributed around a mean of 88.8. The "lowest" rates averaged 81.9, but with the mode falling apparently rather definitely to the left. The difference in the means of average and lowest rates was 6.9. This group also, then, as regards oxygen consumption, is closely similar to the other types, and slightly more consistent in the agreement between average and lowest rates. Whether the difference noted is meaningful and, if so, what the meaning may be are indeterminate.

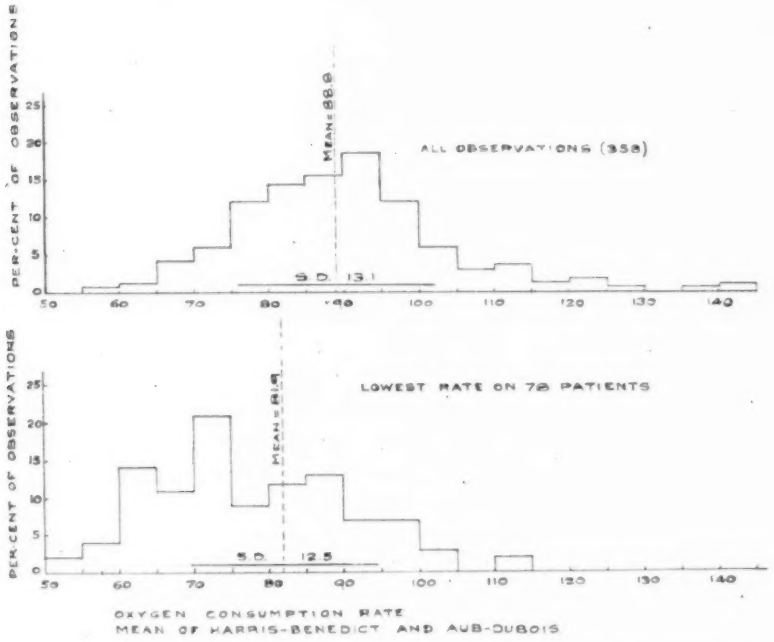

Fig. 11.—Graphs showing respectively the distribution of all determinations and of the lowest rate of oxygen consumption recorded in each of 78 cases diagnosed as schizophrenia, unclassified.

COMMENT

It may be noted that our results in the series of 214 cases herein reported were closely similar to those obtained in the first 80 of the cases previously reported.[3] The average rate of oxygen consumption in the first series was 89.1 per cent of normal, and in the larger series, 88.3 per cent (chart 5). In the first series, the rate in 56 per cent of the cases fell below the level of 90, and in the latter series exactly the same proportion was observed. Likewise, highly indicative of the reliability of the data is the fact that subdividing the cases into kraepelinian groups left the mean of each group closely similar to that

of the total series. Excluding the "simple" type, of which the number was small, the means were: catatonic, 87.9; hebephrenic, 89.4; paranoid, 87.9, and indeterminate, 88.8. Equally convincing is a test based on the average lowest reading obtained, the values being 79.2, 80.6, 80.8 and 82.0 per cent, respectively. The probability of reaching such a degree of consistency as a matter of random chance is so small as to be practically negligible. Such inner consistency is one of the most conclusive of statistical proofs.

Nevertheless, the work of Claude and of Henry as well as our own experience indicates that in schizophrenia the rate of oxygen consumption in any given determination is highly unlikely to represent the true basal rate. Accordingly, the term "basal metabolism" as applied to such determinations is a misnomer. What one is measuring in schizophrenic patients is ordinarily the basal metabolic rate summated with indeterminate increments of oxygen consumption due to psychomotor tension. That the motor discharges to the skeletal muscles (hence oxygen consumption) are constant and minimal, even in the case of the normal subject in repose, is a supposition that cannot be granted by any one familiar, for instance, with the variations in the knee jerk under such conditions. These motor discharges are ordinarily in continual flux, and a true basal condition can be obtained only with considerable training.

There is need for the development of a methodology for obtaining true basal rates, especially in psychotic, but also in nonpsychotic subjects. It is possible that further systematic investigation would disclose some sedative drug that would selectively relieve psychomotor tension but leave undisturbed the physiologic processes on which the true basal rate of oxygen consumption depends. Failing to find such a sedative, one might make shift to use a drug which had a not too extensive but definitely predictable effect on the consumption rate.

An alternative method would be one in which adequate account was taken of the objective indexes of psychomotor tension during the test periods, with a view to correcting the rate as recorded. Some of these indexes are pulse rate, pulse regularity, pulse pressure, depth and regularity of the respiratory excursions, body temperature and degree of regularity of oxygen consumption itself from minute to minute. We now have under study a somewhat extensive body of data from schizophrenic as well as nonpsychotic persons. It is hoped that a multiple regression equation may be derived by which correctional factors may be introduced and the true basal rate more or less accurately estimated. The work of Jenkins,[11] however, as well as our own experience, indi-

11. Jenkins, R. L.: Basal Metabolism: I. The Error of Basal Metabolism Determination and the Normal Range of Basal Metabolism, Arch. Int. Med. **49**: 181 (Feb.) 1932; II. The Basal Pulse Complex, ibid. **49**:188 (Feb.) 1932.

cates that such factors will be difficult to deal with because of the fact that they are inconstant and inconsistent in their manifestations. In individual cases we have noted determinations in which, for instance, a higher pulse pressure was obtained with a lower oxygen consumption test. The best single correctional factor now available is perhaps one derived from the basal pulse complex of Jenkins.

Until a technic for the reliable determination of the basal rate is evolved, investigators, at least in the psychiatric field, would do well to discontinue the use of the term "basal metabolism." It is misleading to the reader and may lead to confused thinking on the part of the investigator.

With all controllable sources of variability eliminated, our patients showed an average difference of 6.2 points between consecutive readings. Since the basal metabolism measures fundamental protoplasmic activity, the true basal rates could hardly have undergone significant change with a few minutes. That single fact establishes a practical certainty that the rates as determined are commonly above the true basal rate. In a nutshell, if one of the recorded rates is higher than the other through the operation of concealed sources of error, it is to be assumed that these same sources of error are operative to displace even the lower reading to an indeterminate extent in an upward direction.

We have made many attempts, by habituating the patients to the technical procedures involved, to reduce the rates to a consistent minimal level. As shown by chart 6, however, after superficial quietude was attained, further rehearsals had no significant effect on the consumption rate. Sometimes the last rate obtained in a series was lower than the first, but in almost as large a number the first rate was the lower.

Our data as they now stand compel the conclusion that any given determination of the rate of oxygen consumption in the schizophrenic patient is antecedently unlikely to indicate at all accurately his actual basal metabolic rate at any given time. In estimating the true rate from studies of variability, the ordinary statistical methods are not applicable. This follows from the fact that commonly the errors are all in one direction, namely, upward. On the reasonable supposition that the lowest rate recorded most nearly approximates the basal rate in each case, it might be stated that an average of 81 per cent is characteristic of schizophrenia. It is likely that when the rate is finally and accurately determined, it will fall below this level.

If one were to make the arbitrary guess that the true basal rate lies below the lowest recorded by an amount equal to the average difference of consecutive readings, the actual basal rate for our series would be about 81.1—6.2 per cent or 74.9 per cent. It is hoped later to make a check on this guess by the introduction of sedation as an experimental

method. Suffice it at this juncture to state that the basal metabolic rate of schizophrenic patients unquestionably falls well below the rate of nonpsychotic subjects.

In addition to the systematic depression of the oxygen consumption rate due to the psychosis, as such, one must also take into account the operation of numerous potentially significant intrinsic variables. These include age, chronicity of the psychosis, lability of mood, habitual level of physical activity and of protein consumption, body temperature, endocrine status, cardiovascular efficiency, season, locality and individual

Statistical Synopsis *

Constants of Distributions of the Oxygen Consumption Rates of Untreated Patients, Various Selections

	No. Patients	No. Readings	Minimum	Maximum	Range	Mean	Standard Deviation	Coefficient of Variation, per Cent
Lowest	214	214	52	117	65	81.1 ± 0.53	11.55 ± 0.38	14.2
Mean	214	214	57	147	90	88.3 ± 0.48	10.41 ± 0.34	11.8
First	214	214	52	152	100	88.0 ± 0.64	13.81 ± 0.45	15.7
Last	214	214	57	137	80	88.3 ± 0.54	11.68 ± 0.38	13.2
Individual range	167	...	2	72	70	21.6 ± 0.78	14.77 ± 0.55	68.4

Constants of the Distributions of All Oxygen Consumption Rates on Schizophrenic Patients by Subclasses

Simple	14	74	67	182	115	95.0 ± 1.33	16.95 ± 0.94	17.8
Hebephrenic	39	192	67	127	60	89.4 ± 0.58	11.84 ± 0.41	13.3
Catatonic	45	191	62	122	60	87.9 ± 0.59	12.09 ± 0.42	13.7
Paranoid	38	163	52	142	90	87.9 ± 0.59	11.21 ± 0.42	12.7
Indeterminate	78	358	57	142	85	88.8 ± 0.47	13.07 ± 0.33	14.7

Constants of the Distributions of the Lowest Basal Metabolic Rates on Schizophrenic Patients by Subclasses

Simple	14	...	67	107	40	85.57 ± 2.45	13.07 ± 1.73	15.2
Hebephrenic	39	...	67	102	35	80.59 ± 0.96	8.93 ± 0.68	11.0
Catatonic	45	...	62	112	50	79.22 ± 1.16	11.53 ± 0.94	14.5
Paranoid	38	...	52	102	50	80.82 ± 1.01	9.23 ± 0.71	11.4
Indeterminate	78	...	57	117	60	81.99 ± 0.95	12.49 ± 0.67	15.2

Constants of the Distributions of the Mean Basal Metabolic Rates on Schizophrenic Patients by Subclasses

Simple	14	...	82	147	65	99.14 ± 2.89	15.48 ± 2.05	15.6
Hebephrenic	39	...	77	102	25	88.54 ± 0.80	7.38 ± 0.56	8.3
Catatonic	45	...	62	112	50	86.00 ± 1.11	10.10 ± 0.78	11.7
Paranoid	38	...	67	102	35	86.34 ± 0.85	7.82 ± 0.60	9.0
Indeterminate	78	...	57	117	60	88.77 ± 0.81	10.60 ± 0.57	11.9

* Table compiled by E. M. Jellinek, chief statistician.

laboratory error. From the findings of Henry,[9] as well as our own experience, it is surmised that there is a high correlation between "moodiness" and the variability of oxygen consumption. The most significant individual variable is probably the depth of the psychosis itself. In Fischer's[7] series the average rate in 30 typical cases was 86.4 per cent, whereas in the "recovered" series it was only slightly under normal, as it was also in the subjects in the initial stage of the disorder. Our own data have not yet been analyzed to show the changes coincident with recovery, but in individual instances we have noted differences between deeply psychotic and "recovered" patients comparable with the differences in the averages reported by Fischer. It is

hoped later to present an analysis of our data, taking into account the variables mentioned. The data as they stand are presented primarily as one item in an organic paradigm of the psychosis.

Comparing the rates of oxygen consumption in the various subtypes of schizophrenia, it is seen that there are no significant differences among them, except perhaps in the case of the "simple" group. There are, however, significant differences in the variability. The hebephrenic and paranoid groups show the smallest standard deviation, while the simple and unclassified show the highest. The most regular curve was obtained in the case of the paranoid group, while all the rest of the groups show suggestions of polymodality. It is interesting and probably significant in this connection that the paranoid group was the only one in which the group diagnoses could be made with approximate precision. In this group alone unanimity of opinion among the psychiatric observers was common. The data, so far as they go, suggest that the paranoid group may constitute a true nosological entity, whereas the other groups are made up of mixtures of improperly differentiated types.

SUMMARY

The rate of oxygen consumption under conventionally satisfactory conditions was determined in 214 male schizophrenic patients. The average was 88.3 per cent of standard normal.

The average age of the group was 30.2 years and the average period of hospitalization at the beginning of each study was 4.4 years.

In the individual cases, from 1 to 15 readings were obtained. Each reading ordinarily represented the lower of a pair determined in consecutive tests. In such pairs the variation between consecutive readings averaged 6.2 points, the first or second being higher in approximately equal numbers.

The average difference between the highest and lowest readings obtained in each patient in the total series was 21.6 per cent, the range being from 2 to 70 per cent. The causes of the difference are discussed.

The average lowest reading obtained in each patient was 81.1 per cent. Evidence is presented that this more nearly represents the true basal rate than does the average mean rate (88.3 per cent).

The rates determined for each subgroup of patients were: catatonic, 87.9 per cent; hebephrenic, 89.4 per cent; paranoid, 87.9 per cent; simple, 95.0 per cent, and indeterminate, 88.8 per cent. There is a suggestion of polymodal distribution in all but the paranoid group that casts doubt on their nosological homogeneity.

Comment is offered that the high degree of consistency between the results of this study and the results in 80 of the cases previously reported, as well as the consistency among the subgroups, establishes the statistical reliability of the data.

The need for a standardized sedative or for the development of reliable correction factors to permit measurements of true basal metabolism in schizophrenia is discussed. The term "basal metabolism" as now used is a misnomer for "oxygen consumption rate."

CONCLUSION

Schizophrenia is a condition characterized, among other physiologic abnormalities, by a systematic downward displacement of the oxygen consumption rate. The data as reported offer no evidence whether the displacement is causative of, consequential to, concomitant with or integral in the psychosis, proper. The report serves chiefly to define a problem for further research.

DEVELOPMENT OF BEHAVIOR PATTERNS AND MYELINIZATION OF TRACTS IN THE NERVOUS SYSTEM

ORTHELLO R. LANGWORTHY, M.D.

BALTIMORE

There is a growing tendency to correlate physiologic with morphologic observations. This gives an important control to experiments requiring operation in which the damage to the central nervous system is often greater than the experimenter realizes. Similarly, in behavior studies, it is interesting to try to connect the appearance of a new pattern with the maturation of cells and fiber tracts in the nervous system. Just as with pathologic studies of nervous diseases, so here the staining methods are often inadequate for demonstrating the morphologic changes. In pursuing developmental studies the maturation of the cells as regards neurofibrils or granules might be observed. The formation of synaptic junctions cannot yet be accurately demonstrated. Myelinization of nerve pathways is one phase of maturation of the neuron that may be followed relatively easily. Myelinization has been used by me as an index of neuron maturity.

Myelinization of the human central nervous system begins in the fourth or fifth month of fetal life and is complete at about the time of puberty. Myelin does not make its appearance in all portions of the nervous system at the same time or simultaneously in all parts of an individual nerve fiber. It occurs first on the portion of the axon close to the cell and slowly spreads out along the fiber. During the last portion of the nineteenth century, many neurologists were studying the sequence of myelinization in the human fetus and the new-born. Paul Flechsig,[1] one of the foremost of these investigators, first observed that tracts become myelinated in a definite sequence, so that fibers belonging to related functional systems become medullated at the same time. This suggested that nerve pathways become myelinated when they become functional, and this assumption has been the basis of recent studies which seek to correlate the medullation of fiber systems in the nervous system with the appearance of new reflex patterns in the organism.

I have followed the development of reflex patterns and myelinization in three mammals: opossum, cat and man. These animals were chosen

From the Subdepartment of Neurology, Johns Hopkins University.

1. Flechsig, P.: Die Leitungsbahnen im Gehirn und Rückenmark des Menschen auf Grund entwicklungsgeschichtlicher Untersuchungen, Leipzig, W. Engelmann, 1876.

for definite reasons. The cat is a common laboratory mammal, often utilized for physiologic studies of the nervous system. There are objections to carrying out the whole program with the cat, for this animal is born when rather mature, and many of its behavior patterns are already functional at birth. In order to follow the coordination of the extremities, for example, it would be necessary to study the animal at still younger stages. Observations on fetal animals present great technical difficulties, in that it is almost impossible to maintain a proper oxygenation of the blood. The opossum is ideal for study of the earlier stages of development, as it is born after a gestation period of twelve days, in an extremely immature condition. The reason for the study of the human material is clear, as it presents such important problems in the field of behavior. The work has been followed for some years and reported elsewhere in detail.[2] It is proposed to give specimens of the types of activity studies and a discussion of certain general principles of myelinization in the nervous system. Since the most immature preparations were opossums, the development of reflexes in this animal will be considered first. In comparing the results of study of the nervous system of these three mammals it must be realized at once that they cannot be thought of as related to one another in a linear way, but that they must be considered as independent offspring of a mammalian stem leading back to a common primitive source. It cannot be emphasized too strongly that all have become specialized in the course of evolution in divergent directions.

OPOSSUMS

The opossums, after a gestation period of twelve days, when scarcely more than 1 cm. long, are able to climb the short distance

2. Langworthy, O. R.: (*a*) A Physiological Study of the Reactions of Young Decerebrate Animals, Am. J. Physiol. **69**:254, 1924; (*b*) The Development of Progression and Posture in Young Opossums, Am. J. Physiol. **74**:1, 1925; (*c*) Relation of Onset of Decerebrate Rigidity to the Time of Myelinization of Tracts in the Brain-Stem and Spinal Cord of Young Animals, Contrib. Embryol. **17**:125, 1926; (*d*) Correlated Physiological and Morphological Studies of the Development of Electrically Responsive Areas in the Cerebral Cortex of the Opossum, Contrib. Embryol. **19**:149, 1927; (*e*) The Histological Development of Cerebral Motor Areas in Young Kittens Correlated with Their Physiological Reaction to Electric Stimulation, Contrib. Embryol. **19**:177, 1927; (*f*) A Correlated Study of the Development of Reflex Activity in Fetal and Young Kittens and the Myelinization of Tracts in the Nervous System, Contrib. Embryol. **20**:127, 1928; (*g*) The Behavior of Pouch-Young Opossums Correlated with the Myelinization of Tracts in the Nervous System, J. Comp. Neurol. **46**:201, 1928; (*h*) Medullated Tracts in the Brain Stem of a Seventh-Month Human Fetus, Contrib. Embryol. **21**:37, 1930; (*i*) Development of Behavior Patterns and Myelinization of the Nervous System in the Human Fetus and Infant, Contrib. Embryol., to be published.

into the pouch (Hartman, 1920).[3] They progress by seizing the hair of the mother with the claws of the forelegs and pulling themselves ahead with alternate movements of these extremities. When they have reached the pouch, they seek for and become attached to a nipple. This is swallowed far down into the pharynx, and for weeks the animals do not relinquish their hold. Their activity during this period is extremely circumscribed.

Young opossums, 7 days old and 27 mm. in length, were removed from the pouch for study. The skin was pink and wrinkled and so thin and transparent that structures underneath were visible. No vibrissae were present on the face; the lateral mouth grooves had not differentiated, and the mouth appeared to be a round hole. No eyeslits had yet appeared. The animals maintained a position of flexion of the whole body and lay on the side. Movements were widespread and consisted of contractions of the musculature of the abdomen and trunk, causing a curving of the body with a bowing of the back. Beats of the fore legs occurred, but there was little contraction of the musculature of the hind leg. If the animals were placed on a piece of gauze, the claws of the fore legs seized the threads, and the young pulled itself along. The musculature was so strong that the animal could support the weight of the body when hanging by one fore leg. The sucking reflex was well developed, and a touch in the region of the face caused sucking movements, the opossum turning toward the stimulating point. Wide side-to-side movements of the head occurred when the animals were active. They obviously represented a search for the nipple.

The mechanisms that guide the new-born animals into the pouch and in contact with the nipple must be of the simplest. Stimuli coincident with birth (air in the lungs, peristalsis of the intestines and cold) may initiate the progressive movements of the legs. Tactile and thermal stimuli probably guide the animal to the softness and warmth of the pouch, and the wide side-to-side movements of the head enable it to find a nipple.

There is no myelinization of the nervous system at birth; little myelin was present in a preparation 49 mm. in length and 36 days old. The ventral roots at this time contain a small number of faintly myelinated fibers; there are no myelinated fibers in the dorsal roots. A few intersegmental fibers are medullated in the ventrolateral columns. In the brain stem some fibers of the medial longitudinal fasciculus are acquiring their myelin sheaths. The vestibulbar nerve is the only cranial nerve that has any medullation. A few cells in the reticular formation give rise to myelinated segmental fibers.

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3. Hartman, C. G.: Studies in the Development of the Opossum, Didelphys Virginiana: V. The Phenomena of Parturition, Anat. Rec. **19**:25, 1920.

The order of development of myelinization in its early stages in the opossum is as follows: The first myelinated fibers in the spinal cord appear in the cervical region, and medullation of the cord progresses in a caudal direction. Just as the ventral roots of the spinal cord show myelinization before the dorsal, so myelinated fibers appear earlier in the ventral gray matter than in the dorsal gray matter. The ventral commissure and short intersegmental fibers receive their myelin early. Fibers extending from the brain into the spinal cord (medial longitudinal fasciculus, reticulospinal, tectospinal and vestibulospinal) are myelinated earlier than afferent pathways from the spinal cord to the brain. In the medulla, the first myelinated fibers occur in the vestibular nerve, the medial longitudinal fasciculus and the axons of cells of the reticular formation. The nerves to the extra-ocular muscles have a few myelinated fibers in advance of the hypoglossal. The glossopharyngeal and vagus nerves early show some myelinated fibers. The midbrain tract of the trigeminal nerve is medullated slightly earlier than the spinal tract. The rubrospinal tracts do not acquire their myelin sheaths till relatively late.

The first medullated fibers to enter the cerebellum are vestibular, and most of them end in the roof nuclei. It is only later that myelinated fibers extend into the anterior and posterior portions of the vermis and then into its mesial portion. Still more time elapses before myelinated fibers are seen in the hemispheres. Of particular interest is the fact that medullated fibers are found in considerable numbers in the brachium conjunctivum before any myelinization has occurred in the hemispheres and only slight myelinization in the vermis. The great cerebellar efferent pathways are myelinated before the cerebellar afferent pathways.

The corticospinal fibers are very slow in acquiring their myelin sheath. The same may be said of the medial lemniscus. Fibers from the thalamus become medullated and extend into the cortex of the cerebral hemispheres before the corticopontile and corticospinal fibers acquire their myelin sheaths.

If the myelinization of tracts is correlated with the development of activity, it is found that the righting reflexes appear at a time when the medial longitudinal fasciculus, reticulospinal, tectospinal and vestibulospinal tracts become myelinated. With myelinization of the ventral commissural fibers of the cord there is an improvement in the coordination of the extremities. As medullation proceeds caudad in the cord, the movements of the hind legs become coordinated with each other and with those of the fore legs. The movements of the animal become less ataxic, steadier and better coordinated when the cerebellar connections become myelinated. About six weeks after birth, when opossums

begin to leave the pouch to cope with the environment outside, new behavior patterns develop rapidly, and the deposition of myelin is accentuated.

In the case of the opossum it is clear that well coordinated activity occurs before the organism as a whole is well differentiated. At an embryonic stage of development, it breathes and produces an adequate oxygenation of the blood, so that its reactions may be observed without discounting the effects of asphyxia. Complicated activity is carried out by this animal before there are any myelinated fibers in the nervous system.

FETAL AND YOUNG KITTENS

Tilney and Casamajor [4] studied the reactions of young kittens and the myelinization of tracts in the central nervous system. They concluded that it was possible to consider that all the behavior patterns present at birth were mediated along reflex arcs already myelinated. My observations confirmed and amplified those of Tilney and Casamajor.

The behavior of six fetal kittens near term, from 105 to 150 mm. in crown-rump length, was studied. In all of the fetal kittens there were myelinated fibers in the spinal cord; in none did afferent sensory paths show the presence of myelin as high as the brain stem. But myelinated fibers from the brain stem did run down into the spinal cord in the medial longitudinal fasciculus, reticulospinal, tectospinal and vestibulospinal tracts. Even in the youngest fetal kitten, the intersegmental fibers of the cord showed considerable myelinization, and the ventral roots showed definite myelinated fibers. The only objection to explaining the activity of the fetal kittens on the basis of medullated pathways would seem to be that the afferent spinal fibers are relatively slow in becoming myelinated, although, even in the youngest fetal kitten, the dorsal roots showed slight but unmistakable signs of myelin.

The leg of the fetal kitten was withdrawn by pinching the foot; this is a local reflex that could be mediated by myelinated spinal fibers. The scratch reflex obtained from the fetal kittens may similarly be considered a purely spinal reflex, although it may be influenced by afferent impulses carried through the trigeminal fibers, which are becoming medullated. The rotation of the body seen in some of the fetal kittens depends on influences carried to the spinal cord by vestibulospinal fibers or through the medial longitudinal fasciculus.

The progressive movements of the fetal kittens were poorly coordinated; alternate progressive movements of the fore legs occurred, but the hind legs moved little and then synchronously in a bilateral, extensor thrust. The rostral portion of the spinal cord showed the greatest mye-

4. Tilney, F., and Casamajor, L.: Myelinogeny as Applied to the Study of Behavior, Arch. Neurol. & Psychiat. **12**:1, 1924.

linization, the number of myelinated fibers decreasing progressively in a caudal direction. Reactions could be obtained from the fore legs more easily and more accurately than from the hind legs and tail.

In the new-born kitten the righting reflex is developed. This is but an amplification of the rotation of the fetal kitten which has become more effective. With the development of better coordination in the young animals, further medullation of spinal roots and tracts occurs. The ataxia so prominent in the new-born disappears when the cerebellar afferent and efferent pathways become medullated. The postural reflex becomes operative in kittens of 9 and 10 days; at this time myelinated rubrospinal fibers may be seen in the spinal cord. The corticospinal fibers show traces of myelin in the kitten of 11 days.

The pathways in the central nervous system become myelinated in approximately the same order in the three mammals, opossum, cat and man. The progression of myelinization will therefore be discussed in connection with the human fetus. Study of the cat suggests that myelinated pathways may carry the stimuli eliciting all the behavior patterns present in the new-born and young animals.

HUMAN MATERIAL

I now have sets of serial sections of the brain stem of the sixth, seventh and eighth month human fetus and of an infant 2 months old. Four sets of sections of the new-born that had been described by Sabin[5] were examined to complete the series. All these brain stems give the picture of myelinization present in human beings and are not necessarily typical for different ages, but they do illustrate the order of acquisition of myelin. Somewhat younger specimens would give further information concerning the first appearance of myelin. On the other hand, preparations older than those described would give few data, as almost all of the tracts of the brain stem have acquired some myelin in early infancy, and the process continues as an increase in the diameter of the sheath on the individual fibers. A summary of the findings will now be given.

The Human Fetus of Six Months.—The fetus was 235 mm. in crown-rump length and weighed 1,045 Gm. The estimated age was 26 weeks. While there is a considerable amount of myelin in the cervical portion of the spinal cord, it decreases progressively toward the lumbar portion. The ventral and dorsal roots are well myelinated. The fibers of the ventral commissure stain only lightly. The intersegmental fibers of the ventrolateral columns are acquiring myelin

5. Sabin, F. R.: (*a*) An Atlas of the Medulla and Midbrain, Baltimore, Friedenwald Co., 1901; (*b*) Description of a Model Showing the Tracts of Fibers Medullated in a New-Born Baby's Brain, A. J. Anat. **11**:113, 1911.

sheaths; they stain more deeply in the cervical portion of the cord. The spinocerebellar tract of Flechsig is conspicuous, owing to the myelin on the fibers. The tractus cuneatus stains well, but there is much less myelin on the fibers of tractus gracilis.

The optic and olfactory nerves show absolutely no myelinization. The oculomotor, trochlear, abducens and hypoglossal nerves all have a faint amount of medullation, which varies from one to another. The abducens nerve stains most deeply, perhaps because it is in closest relation with the vestibular mechanism. The motor and sensory roots of the trigeminal nerves may be followed into the brain stem; the motor root stains more deeply than the sensory. The facial nerve can be followed in its course through the medulla by the myelinization of its fibers. The vestibular portion of the acoustic nerve is much more heavily myelinated than the cochlear portion. The vestibular fibers are conspicuous structures in the medulla, and the pathways are myelinated into the medulla and into the medial longitudinal fasciculus and into the vestibulospinal tract. The cochlear nerve and nuclei take a rather faint myelin stain, but the secondary cochlear fibers show traces of myelin as high as the acoustic colliculus in the midbrain. The other three cranial nerves, glossopharyngeal, vagus and accessory, show very little medullation. The tractus solitarius may be identified.

The medial longitudinal fasciculus is the most conspicuous group of myelinated fibers in the brain stem. The fibers may be followed throughout almost their entire course in one sagittal section; from the ventral surface of the spinal cord the tract bends dorsally to occupy a position just ventral to the hypoglossal, abducens, trochlear and oculomotor nuclei, and terminates in the nucleus of the posterior commissure. The vestibulospinal tract is well myelinated, and the fibers of the reticulospinal tract have also acquired myelin sheaths. The tectospinal, rubrospinal and corticospinal tracts and the medial lemniscus are completely nonmedullated. The spinocerebellar tract of Flechsig is myelinated into the cerebellum. No myelinated fibers connect with the inferior olive.

The afferent myelinated fibers to the cerebellum come from the vestibular nerve and vestibular nuclei, and also from the spinocerebellar tract of Flechsig. The spinocerebellar fibers enter the vermis, while the vestibular fibers end around the cells of the roof nuclei. Some of the axons from the cells of these nuclei are myelinated and leave the cerebellum to terminate in the vestibular nuclei. In addition, a few myelinated fibers from the nucleus emboliformis leave the cerebellum through the brachium conjunctivum and extend down into the midbrain, where they lose their myelin sheaths. There are no medullated tracts rostral to the midbrain.

If tracts become functional when they become medullated, the fetus of 6 months would not be able to carry on the essential activity

of life. There is very incomplete medullation of the tracts controlling respiration and deglutition.

Human Fetus of the Seventh Month.—Here again it was found that there was almost no trace of myelinated connections anterior to the midbrain. The exceptions are a few myelinated fibers in the region of the globus pallidus and a few fibers of the medial lemniscus and spinothalamic tracts myelinated into the region of the thalamus.

Of the descending paths from the brain stem to the spinal cord, the vestibulospinal, reticulospinal, tectospinal and medial longitudinal fasciculus are partially myelinated. The spinocerebellar tracts of Flechsig and Gowers contain medullated fibers that can be followed through the brain stem to the vermis of the cerebellum; spinothalamic fibers lose their myelin sheaths before they reach the thalamus. In the posterior columns the cuneate tract is well medullated, but there are few myelinated fibers in the tractus gracilis. The tractus cuneatus may be followed to the nucleus cuneatus, and from this nucleus myelinated internal arcuate fibers cross the midline to form the medial lemniscus. These fibers are not medullated to their termination in the thalamus.

The cortex of the cerebellar vermis of the seventh month fetus receives myelinated fibers, but none extends into the cerebellar hemispheres. Spinocerebellar and vestibulocerebellar fibers are medullated. No myelinated fibers enter the flocculus. The corpus restiforme may be traced rostrad of the dentate nucleus to the cortex of the vermis. As regards the deep cerebellar nuclei, the nuclei of the roof, nucleus globus and nucleus emboliformis give rise to myelinated fibers. The roof nuclei make both afferent and efferent connections with the vestibular nuclei. Fibers from the emboliform nucleus are myelinated when they leave the cerebellum through the brachium conjunctivum, but lose their myelin in the midbrain before they reach the red nuclei. The cells of the dentate nuclei give rise to no medullated fibers.

Myelinization in the seventh month human fetus is limited largely to structures in the midbrain, medulla and cord. All the pathways concerned with fundamental activities of the fetus are myelinated. The vagus nerve is myelinated in the medulla. In the spinal cord, well medullated reflex arcs are present. A child born at the end of 7 months has a good chance of survival.

Human Fetus of the Eighth Month.—Even at this time there is a steady decrease in myelinated fibers from the cervical to the lumbar portion of the cord. There are numbers of medullated fibers in the gray matter and in the ventral columns, and the intersegmental fibers stain well. The cuneate tract takes the myelin stain more deeply than the gracile tract. On examining the posterior columns it is evident

that the fibers become myelinated in complicated patterns of separate groups and bundles.

At the eighth month, the cranial nerves connecting with the midbrain and medulla are uniformly well myelinated. The olfactory and optic nerves still show no myelin. Gudden's commissure can be traced across the optic chiasm, owing to a faint medullation of its fibers.

Myelin is becoming deposited on the fibers of the rubrospinal tract close to the cells of origin, but the tract is nonmedullated in the spinal cord. The corticospinal tract is completely nonmedullated. There are a few myelinated tectospinal and tectobulbar fibers. The spinocerebellar tracts of Flechsig and Gowers stain deeply; the medial lemniscus is not medullated as far as the termination of its fibers in the thalamus.

There has been almost no progress of myelinization of the connections of the cerebellar hemispheres, but the connections of the vermis and of the flocculus are now well medullated. There is some myelinization of fibers from the cells of the dentate nucleus; the cephalic portion of the dentate nucleus appears to give rise to more myelinated fibers than the caudal portion. The lateral fibers in the brachium conjunctivum become medullated first. The caudal surface of the red nucleus is covered by a definite capsule of myelinated fibers. No myelinated fibers reach the habenular nuclei, but the cells give rise to the comparatively heavily myelinated fibers of the habenulopeduncular tract

There were only a few faintly myelinated fibers in the corpus striatum of the fetus of the seventh month, and the great advance found in the fetus of eight months is the myelinization anterior to the limits of the midbrain. Fibers connected with the corpus striatum are the structures in the forebrain that first receive sheaths of myelin. The fibers that divide the globus pallidus into distinct portions are becoming myelinated, and fibers throughout the globus pallidus show signs of myelinization. Numbers of fibers cross the internal capsule and form a distinct capsule for the subthalamic nucleus. Indeed, this nucleus contains many stained fibers. It will be noticed, however, that the bundle of fibers from the globus pallidus that swings around the mesial edge of the corpus striatum to the region of the red nucleus shows as yet no signs of myelinization.

Study of the thalamic region demonstrates very few myelinated fibers. Those that form the laminae separating the different divisions of the thalamus have not yet acquired myelin sheaths. The caudal portion of the thalamus contains many more medullated fibers than the cephalic portion. The medial lemniscus fibers are myelinated into the caudal portion of the thalamus; they stain more deeply than the spinothalamic tract and the capsule of red nucleus. Similarly, a few faintly medullated acoustic fibers reach the acoustic lemniscus. No optic fibers

are myelinated. Scattered in the posterior portion of the thalamus are a few medullated fibers which probably connect the different nuclei. No myelinated fibers extend from the thalamus to the cerebral cortex.

In summary, the eighth month fetus shows progress over the seventh month fetus in the medullation of segmental and intersegmental pathways and in further medullation of the cerebellum and corpus striatum. There is still little myelinization in the thalamus.

The Infant Born at Term.—Here the observations made by Sabin [5] and the sections studied by her have been reviewed. The optic nerve begins to be myelinated at the time of birth, but the olfactory fibers and tracts are still nonmedullated. In one specimen the myelinated optic fibers may be followed to the optic geniculate. The medial lemniscus is myelinated to the ventrolateral nucleus of the thalamus, and fibers arising from the cells of this nucleus stain as far as the cerebral cortex. Myelinization of the acoustic pathways has advanced slowly, so that few fibers stain to the level of the acoustic geniculate.

The tectospinal pathway has not completed its medullation, owing to the faintly myelinated connections of the optic colliculus. The corticospinal tract is not medullated at all; the rubrospinal fibers have only a faint covering of myelin in the brain stem. The corpus restiforme carries myelinated spinocerebellar fibers of the tract of Flechsig, fibers from the cells of the posterior column nuclei and vestibular and a few olivocerebellar fibers to the cerebellum. The afferent tracts from the lateral or neo-inferior olive are not yet medullated. There are as yet no medullated pontile fibers. No myelinated fibers are found in the cerebellar hemispheres. The fibers reaching the red nucleus through the brachium conjunctivum form a heavy, medullated capsule on the caudal and ventral surfaces of the red nucleus. A few myelinated fibers from the globus pallidus also reach the red nucleus and form a faintly myelinated capsule on the cephalic side.

The brain of the new-born is distinguished by the increase in myelinated fibers in the thalamus. Myelinated fibers appear in the ventrolateral nucleus and in the optic geniculate. A ventral projection system of fibers extends from the ventrolateral nucleus to the posterior and anterior central gyri of the cerebral cortex. These are the first of the cortical projection fibers to receive their myelin sheaths.

There is at this time a rather uniform degree of medullation throughout the cord, although it is perhaps less marked in the lumbar segments. The fibers in the gray matter and in the ventral commissure stain darkly in all of the sections. The ventral columns are well myelinated, except for small areas on either side of the ventral midline, the position of the corticospinal fibers. Laterally there is no myelinization of the corticospinal and little myelinization of the rubrospinal tract. The fibers of

the posterior columns are all acquiring a covering of myelin, although some portions are more heavily medullated than others.

Brain of an Infant Aged 2 Months.—With birth the process of medullation is greatly accelerated, so that a marked increase in myelin is found in the infant two months after birth. In the cervical portion of the spinal cord there is some myelinization of pyramidal and rubrospinal tracts, but the area that they occupy is a light color. The faintly staining, uncrossed pyramidal fibers occupy a large area in the ventral columns. The spinocerebellar fibers are still stained more deeply than other tracts in the lateral columns and appear an intense black. There is considerable myelin in the lumbar portion of the cord; the ventral portion of the tracts in the posterior column stains more deeply than the dorsal portion. The pyramidal tracts stain very little in the caudal portion of the cord.

The olfactory tracts in the forebrain show the first signs of myelinization at this time. Scattered and faintly myelinated olfactory fibers are found in the secondary olfactory centers in the base of the forebrain, and the tracts in the septum pellucidum and over the surface of the corpus callosum stain lightly. The stria medullaris and stria semicircularis are fairly well myelinated. There are as yet no medullated fibers in the fornix and only the slightest medullation around the mammillary bodies and in the mammillothalamic tract.

The optic nerves, chiasm and tracts are almost completely myelinated, a great advance over the first appearance of myelin in the optic nerve of the new-born infant. There is a heavily myelinated capsule around the optic geniculate, and, from the cells of this nucleus, fibers that stain less deeply enter the internal capsule on their way to the cerebral cortex. The pulvinar contains no myelinated fibers, but a tract of medullated fibers extends around the pulvinar to the optic colliculus and spreads out on the dorsolateral surface of this structure. The deepest layers of the optic colliculus now contain myelinated fibers, and the tectobulbar and tectospinal fibers from this region are acquiring myelin sheaths.

The acoustic geniculate contains myelinated fibers, and projection fibers from the cells are myelinated in the internal capsule. In the thalamus and internal capsule the optic system is now more completely medullated than the acoustic. Thus, the myelinization of the optic fibers has quickly outstripped that of the acoustic fibers, which began far earlier, in at least the sixth fetal month. As regards the other cranial nerves, there is little to be added, as medullation had become relatively complete in the younger series.

There is now myelin on the fibers of the pyramidal or corticospinal tract. In the internal capsule the motor fibers stain less deeply than

the sensory projection fibers in the posterior portion of the posterior limb. Moreover, the temporopontile fibers stain very slighly, so that the corticospinal tract is set off from the more posterior sensory fibers. The frontopontile tract is completely nonmedullated. If the corticobulbar tracts lie in the position in the cerebral peduncle assumed by Dejerine, the mesial group of fibers are not myelinated at all, and only the lateral group can be recognized. The fibers of the rubrospinal tract are very slow in acquiring myelin sheaths, and in the present series they can only barely be recognized in the midbrain and medulla. In this instance the medullation of the corticospinal tract has exceeded that of the rubrospinal tract, which began earlier.

The thalamo-olivary fibers may for the first time be recognized by their light staining. There has occurred a medullation of the axons from the cells of the lateral portion of the inferior olive. These fibers enter the corpus restiforme and are distributed to the cerebellar hemispheres. Marked advances in myelinization have appeared in the cerebellar hemispheres. The pontocerebellar fibers have begun to receive myelin sheaths before the frontopontile and temporopontile tracts are medullated.

The anterior nucleus of the thalamus contains no myelinated fibers, but the stria medullaris, curving around its ventral edge, gives the appearance of a medullated capsule. The medial nucleus of the thalamus contains no evidence of myelinization. The ventral nucleus, on the other hand, stains rather uniformly gray to black. Myelinated spinothalamic fibers end in the ventral nucleus, as do also fibers of the medial lemniscus and brachium conjunctivum. In their turn the cells of the ventral nuclei give medullated projection fibers to the internal capsule. The centrum medianum of Luys and the nucleus semicircularis contain as many medullated fibers as the ventral nucleus. The lateral nucleus of the thalamus and the pulvinar are completely nonmedullated.

COMMENT ON THE PROCESS OF MYELINIZATION

Flechsig showed that in the human fetus and infant the process of myelinization followed a definite pattern. This is certainly true, and after a study of a comparative series it is now plain that tracts are myelinated in practically the same order in all mammals. The order of medullation of tracts in the nervous system of the opossum was the same as that observed in the cat and in man. The previous description makes this clear.

In the spinal cord the motor roots are myelinated before the sensory. The intersegmental, correlation fibers are the first in the cord to acquire myelin sheaths. Later, the commissural fibers are medullated and then the long pathways. It is curious that certain efferent tracts from the

brain stem are myelinated before the afferent fibers extending from the spinal cord to the brain stem. The dorsal spinocerebellar is the first long afferent pathway to be myelinated.

It is also worthy of note that myelinization in the region of the spinal cord begins in the cervical region; at an early stage of development the cervical cord shows more myelin than any other portion of the nervous system. This brings to mind Child's theory of axial gradients. Child has endeavored to show that the anterior portion of axial organs are dominant in initiating and controlling the activity of the remainder. Other workers have shown that, from the point of view of embryology, there is a center of dominance in the cervical portion of the cord, and from this region waves of cell division and cell maturation proceed in a caudal direction.

In the brain stem the vestibular nerve is precocious in medullation and in the medullation of its connections, and seems to set the pace of myelinization in this region. From the phylogenetic point of view the vestibular mechanism is early developed, and in the embryo the first groups of cells in the medulla to differentiate are destined for vestibular functions. So it is with myelinization. Two of the three first tracts to be myelinated, extending from the medulla into the cord, the vestibulospinal and medial longitudinal fasciculus, carry vestibular impulses. The vestibular are the first myelinated fibers to penetrate into the region of the cerebellum. The vestibular activity may affect the myelinization of the cranial nerves, for the abducens is the earliest of the motor nerves in the medulla to acquire myelin.

In the brain the process of medullation extends from the medulla in a cephalic direction. This is illustrated in the description of the human fetus and infant. In the sixth month fetus the spinal cord and medulla show some myelinated fibers; in the seventh month, medullation has extended to the upper end of the midbrain. The corpus striatum shows beginning myelinization at 8 months, the thalamus at term, and the process is extending well into the cortex in an infant 2 months of age. Material from the medulla of the eighth month human fetus is excellent for the demonstration of pathways, and particularly to show that the brain stem is built on a segmental basis, with large correlation centers superimposed on this fundamental framework.

Some myelinization of the oculomotor, trochlear, abducens and hypoglossal nerves is present in the sixth month fetus; of these, the abducens nerve shows the greatest amount of myelin and the hypoglossal nerve the least. Except for the vestibular nerve, the motor portions of the cranial nerves are myelinated before the sensory. This is true of the trigeminal nerve. The facial nerve is myelinated early. The cochlear fibers always lag behind the vestibular as regards medullation of the axons.

Certain efferent tracts from the brain stem to the spinal cord are myelinated before the afferent tracts to the brain stem. These efferent pathways are reticulospinal, vestibulospinal and medial longitudinal fasciculus. The two latter are influenced by the early maturation of the vestibular system. In the seventh month fetus the fibers of the medial lemniscus are myelinated to the level of the midbrain but are nonmedullated above that level.

The fact that pathways in the nervous system become myelinated in the order in which they are developed phylogenetically is seen clearly in the case of the cerebellum. In the seventh and even in the sixth month fetus myelinated spinocerebellar and vestibulocerebellar fibers end in the vermis. At that time the cells of the medial cerebellar nuclei give rise to myelinated fibers ending in the vestibular nuclei, and from the nucleus emboliformis a few myelinated fibers enter the brachium conjuctivum. It is not until after birth in the human being that myelinization occurs in the cerebellar hemispheres. The cerebellar hemispheres are new phylogenetic acquisitions, and just as they develop coincidentally with the cerebral hemispheres, so are they myelinated at the same time.

Although the motor nerves receive myelin sheaths before the sensory, in many correlation centers afferent systems are myelinated before the efferent. This is true of the cerebral cortex and also of the cerebellar. It can hardly be considered a universal rule. Thus the habenulopeduncular tract is heavily medullated long before any myelinated fibers reach the cells of the habenular nucleus. The order of myelination shows strange anomalies. Thus, the pontocerebellar fibers are myelinated earlier than the frontopontile and temporopontile fibers.

Once a tract has begun to show myelin on its fibers, the process of myelinization does not necessarily continue at a uniform rate, and the amount of myelinization in another tract beginning later may become more marked. The cochlear connections in the brain stem are well myelinated to the level of the acoustic colliculus in the human fetus of the seventh month; the optic tracts begin myelinization at the time of birth. But the optic connections in the thalamus and the optic projection fibers to the cerebral cortex are myelinated before the acoustic fibers. Thus, the medullation of optic fibers, once it has begun, exceeds that of the acoustic pathways, which began much earlier.

Embryologists have noted that the division and maturation of cells in the nervous system do not go on at a uniform rate, but that there appear to be marked pulses or waves of cell development. This applies also to myelinization. A tract faintly myelinated may remain in this condition for a considerable time before further myelin is deposited on the fibers. Medullation of new groups of fibers may be in abeyance for considerable periods of time, and then whole functional systems become myelinated at the same time.

Birth in the case of man serves as a great stimulus to the deposit of myelin in the nervous system. In the first few weeks after birth the optic and olfactory systems acquire myelin sheaths, and myelinated projection fibers from the thalamus extend to many areas of the cerebral cortex. The question arises as to the changes at birth that account for this increase in the deposit of myelin. Probably it is the result of increased stimulation of the sensory organs.

There is evidence in the case of the human material to suggest that sensory pathways are myelinated at the time when the sensory endings receive adequate stimuli. The sensory endings in the skin and on the muscle and the vestibular and even the cochlear nerves may receive adequate stimuli in utero. The optic and olfactory nerves, however, could scarcely be stimulated until after birth, and myelinization of their fibers does not occur until that time. Moreover, the increased number of stimuli applied to all sensory endings after birth could well account for the accentuation of the myelinization at that time. One objection to this hypothesis has been found. In the guinea-pig, an animal born when very mature, the optic tracts are myelinated at birth.

There is undoubtedly a great variation in the time of myelinization of pathways in different individuals. The material available is much too small in amount to show this variation and demonstrates only the sequence of myelinization. Donaldson [6] has shown that in the rat the nutrition of the animal has no relationship to the time of medullation of the nervous system. Once the process of myelinization has begun, it continues for years, with a gradual increase in the diameter of the sheath of individual fibers.

There are other opinions concerning the process of myelinization. Von Monakow [7] thought that the relative vascularity in different portions of the brain was a more important factor in the development of myelinization than the assumption of function by the nervous pathways.

C. and O. Vogt [8] suggested that the caliber of the fiber was important; the large axons received myelin sheaths late. Important exceptions are at once evident to one familiar with this subject. For example, the tract of Lissauer in the spinal cord contains many finely myelinated fibers. These are not medullated until late, at a time when the corticospinal pathway is becoming medullated.

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6. Donaldson, H. H.: The Effect of Underfeeding on the Percentage of Water, on the Ether-Alcohol Extract and on Medullation in the Central Nervous System of the Rat, J. Comp. Neurol. **21**:139, 1911.

7. von Monakow, C.: Ueber die Projektions- und Associationszentren im Grosshirn, Monatschr. f. Psychiat. u. Neurol. **8**:405, 1900; Demonstration von makro- und mikroskopischen Präparaten, Neurol. Centralbl. **29**:110, 1910.

8. Vogt, C., and Vogt, O.: Die myelo-architektonischen Rindenfelder des Menschen, Neurol. Centralbl. **27**:137, 1908.

Kappers [9] believed that myelinization of a nerve fiber occurs at a time when impulses first begin to travel along the fiber. He based this belief largely on the work of Herman, who placed a piece of a peripheral nerve from a frog in a constant current in a line connecting the electrodes, which remained, however at a distance. There was a vigorous flow of the myelin to the anodal end of the nerve fiber, where it collected in a mass. The tendency of myelin to move in the direction of the anode was clearly proved by this experiment.

While myelinization is one indication of the maturation of the neuron, the data at hand are not sufficient to demonstrate that the deposit of myelin is coincident with the development of function in the neuron. Further work may elucidate the relationship of myelinization to the activity of the nerve cell.

Other morphologic methods have been used to correlate the appearance of behavior patterns with maturation of the nervous system. Craigie [10] studied the differentiation of vascular patterns in the nervous system. Windle [11] correlated the growth of the neurophil in the gray matter of the spinal cord with the activity of kittens. Langworthy [12] studied the the maturation of cells in the cerebral motor cortex and the first responses to electrical stimulation.

ACTIVITY OF HUMAN FETUS AND INFANT CORRELATED WITH MYELINIZATION

Minkowski [12] and others have studied the reactions of the human fetus; probably observations have been made on over fifty fetal preparations of less than 6 months. The work of Minkowski was particularly fortunate in that the specimens were removed at hysterectomy, which was performed under local anesthesia. There was no question of the effects of anesthesia in the case of the preparations. The fetus was immediately placed in a bath of physiologic saline solution heated to 37 C.

Spontaneous movements of the arms and legs were observed in fetal preparations of the second month. In those of the third month other spontaneous activity was seen, such as isolated contractions of

9. Kappers, C. U. A.: Further Contributions on Neurobiotaxis, J. Neurol. **27**:261, 1916.

10. Craigie, E. H.: Changes in Vascularity in the Brain Stem and Cerebellum of the Albino Rat Between Birth and Maturity, J. Comp. Neurol. **38**:27, 1924.

11. Windle, W. F.: Normal Behavioral Reactions of Kittens Correlated with the Postnatal Development of Nerve Fiber Density in the Spinal Gray Matter, J. Comp. Neurol. **50**:479, 1930.

12. Minkowski, M.: Réflexes et mouvements de la tête, du tronc et des extrémités du foetus humain pendant la première moitié de la grossesse, Comp. rend. Soc. de biol. **83**:1202, 1920.

the temporal and the intercostal muscles and isolated movements of the fingers, with trembling of the thumb. In all these preparations there was tonus in the extremities, which maintained them in a determined position and returned them to this position after they had been moved. The preparations of 3 and 4 months showed tonic reflexes, probably depending on sensory stimuli from the cervical region and produced by changes in the position of the head in relation to the trunk. A fetus of 2½ months showed movements of the head, trunk and extremities. These included rotation, raising and lowering of the head, flexion and extension of the trunk and rotation, abduction, adduction, flexion and extension of the extremities. These movements were slow, asymmetric, arrhythmic, incoordinated; of small amplitude and often of a choreiform character.

Inasmuch as myelinization does not begin until the fifth fetal month, it is obvious that all these responses are carried over nonmedullated pathways. There is another consideration in connection with these observations and that is the problem of asphyxia. The umbilical cord is severed at the time of the operation, and want of oxygen must be felt at once. Motor cells throughout the nervous system are stimulated by increased carbon dioxide in the blood, and the reactions of the fetal preparations may be largely, if not entirely, due to this stimulation of the cells. Certainly the observations are made under abnormal conditions.

There have been almost no observations on the human fetus during the latter months of gestation. The activity of the new-born infant may be summarized in the words of Blanton (1917):

> During the first twenty minutes of life may be observed, sneezing, crying, tears, sucking at the nipple, fixation on light, putting the thumb in the mouth, jumping to loud sounds, grasping, following a moving hand with the eyes, turning the head in such a way as to get air when placed on the face, turning over with slight aid, erection of the penis and crying.

There is no need to enter into all the assets of the new-born infant in terms of responses to stimuli and reflex pattern. It is well known that the responses of the infant to stimulation are extremely diffuse. Gradually, well defined patterns of reaction are developed and differentiated; during this time the myelinization of pathways in the nervous system is proceeding rapidly. It is possible to consider that all the activity of the new-born infant is mediated along medullated pathways.

SUMMARY

Reflex activity may be observed for a considerable period before any pathways are myelinated in the nervous system. Pathways become myelinated in the order in which they are developed phylogenetically.

In the three mammals studied the order of myelinization of tracts was similar. Myelinization in the spinal cord begins in the cervical region and progresses caudad; in the brain it begins in the medulla and progresses cephalad. Myelinization appears to occur in waves or pulses and not at a uniform rate; pathways that begin to be myelinated late may complete the process before other pathways that showed some myelin earlier. Birth serves as a great stimulus to the deposit of myelin in the nervous system. There is some evidence that sensory pathways are myelinated at a time when sensory endings receive adequate stimuli. There is not sufficient proof that the deposit of myelin is coincident with the development of function in the neuron.

EFFECT OF EXPERIMENTAL HEPATIC DAMAGE ON THE HEMATO-ENCEPHALIC BARRIER

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A relationship between the gastro-intestinal tract, especially the liver, and the central nervous system is suggested by the demonstration of damage to the liver in diseases usually considered primary to the central nervous system, by the constant association of pathologic processes in the liver and in the brain or cord in such conditions as Wilson's progressive lenticular degeneration and the pseudosclerosis of Westphal, and by the occurrence of clinical and histologic changes in the central nervous system in primary hepatic conditions.

Rapoport [1] stated that diffuse parenchymatous degeneration of the brain, especially marked in the cortex, occurs in acute yellow atrophy; Kirschbaum [2] reported diffuse changes in the central nervous system in atrophy of the liver, and Weltman [3] has also noted pathologic processes of the central nervous system in disease of the liver. Experimentally, the neurologic symptoms occurring in dogs with Eck fistulas when intoxicated with meat are well known. Matthews [4] has reported that a chronic nervous disorder somewhat resembling multiple sclerosis may occur in chronically intoxicated dogs with Eck fistulas that have survived for from ten to twelve months. Pinkussen [5] found meningo-encephalitis in these animals. Fuchs [6] reported one dog with an Eck fistula that was intoxicated with meat and died seventeen days after operation. A clinical diagnosis of encephalitis could be made before death, and microscopic examination revealed a disseminated meningo-encephalitis. One of us (Dr. Crandall) has observed motor paralyses and ataxias in a number of these animals after intoxication with meat;

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1. Rapoport, P. [illegible] Ztschr. f. d. ges. Neurol. u. Psychiat. **126**:473, 1930.
2. Kirschbaum, quoted by Lapinsky, M.: Deutsche Ztschr. f. Nervenh. **97**:95, 1927.
3. Weltman, O.: Wien. med. Wchnschr. **77**:831, 1927.
4. Matthews, S. A.: Am. J. Physiol. **29**:xvii, 1912.
5. Pinkussen, quoted by Lapinsky, M.: Deutsche Ztschr. f. Nervenh. **97**:95, 1927.
6. Fuchs, A.: Wien. med. Wchnschr. **71**:710, 1921.

the symptoms after feeding with meat were transient at first, but became permanent after repeated intoxications. In this connection one should also consider the relationship between achylia gastrica and combined degeneration of the cord. Chevassut [7] has reported decreased function of the liver in about 70 per cent of the cases of multiple sclerosis. Crandall and Cherry [8] found an olive oil lipase in the blood of patients with multiple sclerosis, which they believe is indicative of damage to the liver.

Lewantovsky [9] recently reported a study of the hemato-encephalic barrier in experimental damage to the liver. Cyanol, neutral red and ferric oxysaccharide appeared in the cerebrospinal fluid in phosphorus poisoning and after establishment of Eck fistulas, one dog being tested with each substance. In one dog with ligation of the hepatic artery and in two with a denervated liver, ferric oxysaccharide appeared, but cyanol and neutral red did not come through. Tests were made from one to ten days after operation. These substances were not found in spinal fluid from a control series; the number of controls was not stated. If such a correlation between meningeal permeability and hepatic dysfunction could be substantiated, it would be highly significant. Therefore, we have studied the permeability by various methods in a series of dogs with Eck fistulas and with ligation of the common bile ducts.

Methods used for the study of the hemato-encephalic barrier may be divided into two general classes: first, the determination in the cerebrospinal fluid of substances occurring normally in the blood; second, the introduction into the body of foreign substances and the determination of their appearance in the cerebrospinal fluid or of their relative concentrations in blood and fluid. Of such substances, dyes such as trypan blue, congo red, methylene blue (methylthionine chloride, U. S. P.), bismarck brown, neutral red and fluorescein have been frequently used. In 1925, Walter [10] introduced the use of the bromide ion.

METHODS

Since Lewantovsky [9] based his findings on the results of injections of dye, we have used bromsulphthalein, phenolsulphonphthalein and neutral red. We have also used potassium iodide, Walter's bromide method and a determination of the inorganic phosphorus of the cerebrospinal fluid. In making use of the dyes and of the potassium iodide, the dogs were anesthetized with pentobarbital sodium, and the material was injected into the saphenous vein. Bromsulphthalein was given in

7. Chevassut, K.: Lancet **1**:552 (March 15) 1930.

8. Crandall, L. A., Jr., and Cherry, I. S.: Blood Lipase, Diastase and Esterase in Multiple Sclerosis, Arch. Neurol. & Psychiat. **27**:367 (Feb.) 1932.

9. Lewantovsky, M. I.: Ztschr. f. d. ges. Neurol. u. Psychiat. **126**:484, 1930.

10. Walter, F. K.: Ztschr. f. d. ges. Neurol. u. Psychiat. **95**:523, 1925.

doses of 350 mg. per dog; phenolsulphonphthalein in amounts of 18 mg.; neutral red, 200 mg. per dog, and potassium iodide, 100 mg. per kilogram. Just prior to injection of the substance a cisternal puncture was made, and the needle was left in situ while samples were taken over a period of from two to three hours. Passage of the dye was determined by inspection; the iodide ion was tested as recommended by Cohen.[11] Two normal dogs and one with an Eck fistula received injections of bromsulphthalein; two normal dogs and one with an Eck fistula received injections of phenolsulphonphthalein; three normal dogs and three with Eck fistulas received injections of neutral red, and two normal dogs and one with an Eck fistula received injections of potassium iodide.

TABLE 1.—*Appearance of Dyes and Iodide in Cerebrospinal Fluid After Intravenous Injection*

Substance	Dog	Weight in Kg.	Dose	Time of Cerebrospinal Fluid Examination	Results
Bromsulphthalein	Normal 1	8.6	350 mg.	5, 20, 30, 45 min.	Faint trace at 20, 30, and 45 min.
	Normal 11	13.6	350 mg.	20-30 min. intervals for 3 hrs.	All 8 samples negative
	Eck 27 Op. 6 wks.	15.4	350 mg.	15 min. intervals for 75 min.	All 5 samples negative
Phenolsulphon-phthalein	Normal 4	6.6	18 mg.	15-30 min. intervals for 2 hrs.	All 5 samples negative
	Normal 18	10.9	18 mg.	10-15 min. intervals for 2 hrs.	All 9 samples negative
	Eck 28 Op. 3 wks.	11.4	18 mg.	10-20 min. intervals for 2 hrs.	All 8 samples negative
Neutral red	Normal 17	13.6	200 mg.	15-60 min. intervals for 4 hrs.	Doubtful negative first hr., all others negative
	Normal 21	7.7	200 mg.	15-60 min. intervals for 4 hrs.	Slight trace all samples up to 2 hrs., very slight trace 3 hrs.
	Normal 22	16.3	200 mg.	15-60 min. intervals for 4 hrs.	All 11 samples negative
	Eck 33 Op. 8 wks.	12.0	200 mg.	15 min. intervals for 3 hrs.	All 12 samples negative
	Eck 34 Op. 4 wks.	10.2	200 mg.	15 min. intervals for 3 hrs.	All 12 samples negative
	Eck 35 Op. 3 wks.	15.9	200 mg.	15 min. intervals for 3½ hrs.	All 14 samples negative
Potassium iodide	Normal 9	13.6	1.36 Gm.	5-20 min. intervals for 1½ hrs.	Doubtful negative in 3 first samples
	Normal 10	9.2	0.92 Gm.	15 min. intervals for 3 hrs.	10 of 12 samples doubtful negative
	Eck 27 Op. 9 wks.	14.5	1.45 Gm.	15 min. intervals for 2 hrs.	All 8 samples negative

The permeability quotient of the meninges was determined by the bromide method of Walter,[10] as modified by Gordy and Smith,[12] on seventeen normal dogs (twenty-three determinations), on six dogs with Eck fistulas (seven determinations), and on two dogs with complete obstruction of the common bile duct. On four of the dogs with Eck fistulas, control determinations were made preoperatively, and the test was repeated fourteen days after the establishment of the fistulas. Blood and cerebrospinal fluid were taken as usual on the fifth or sixth day after the beginning of the administration of bromide; blood was obtained without anesthesia from the saphenous or jugular vein; cisternal puncture was performed under local anes-

11. Cohen, H.: Lancet **1**:127 (Jan. 19) 1924.

12. Gordy, S. T., and Smith, S. M.: Permeability of Hemato-Encephalic Barrier as Determined by Bromide Method Arch. Neurol. & Psychiat. **24**:727 (Oct.) 1930.

thesia. As a check on the method, determinations in some cases were made two, four, seven, eight and ten days after the beginning of the administration of bromides.

Cohen [13] suggested that the inorganic phosphorus of the cerebrospinal fluid may be an index of permeability, although the blood phosphorus is too variable to allow of the establishment of a permeability quotient. Determinations of the serum and cerebrospinal fluid phosphorus were made simultaneously on thirteen normal dogs and on six dogs with Eck fistulas, the method of Fiske and Subbarow [14] being used. Filtrate was obtained from the cerebrospinal fluid by treating 5 cc. of it with 2 cc. of 10 per cent trichloracetic acid. Blood and fluid were obtained as for bromide determinations, except in two cases in which pentobarbital sodium anesthesia was used.

The results are presented in tables 1, 2 and 3.

COMMENT

Since the significance and interpretation of our results rest solely on the assumption that the methods employed are capable of accurately measuring changes in meningeal permeability, it is well to examine this assumption. Of the large number of papers dealing with the hemato-encephalic barrier that have been published recently, only a few have viewed in a critical light the methods employed. Loberg [15] has carefully analyzed the significance of the ratio between the concentration of a foreign substance in the blood and in the cerebrospinal fluid, using salicylic acid. He found that the acid first appears in the cerebrospinal fluid when it reaches a concentration of 250 mg. per hundred cubic centimeters in the blood, and that its concentration in the cerebrospinal fluid is a function of blood concentration and not of the hemato-encephalic barrier. As a general rule, the higher the blood concentration, the lower the "permeability quotient." He discussed the variables, rate of absorption, rate of excretion and composition of the blood, which may affect the blood concentration of a perorally administered substance and its ability to penetrate the meninges. On the other hand, Walter has consistently maintained,[10] on the basis of considerable experimental work, that the absolute concentration of the substance (bromide) in the blood or in the cerebrospinal fluid has no significance, and that despite variations in blood concentration the quotient remains constant. Inflammatory meningitis is perhaps the condition in which the barrier function of the meninges is most obviously decreased; in this condition dyes pass with relative rapidity into the fluid,[16] and the "permeability

13. Cohen, H.: Quart. J. Med. **17**:289, 1924.

14. Fiske, C. H., and Subbarow, Y.: J. Biol. Chem. **66**:375, 1925.

15. Loberg, K.: Ztschr. f. d. ges. Neurol. u. Psychiat. **115**:308, 1928.

16. Bonar, B. E., and Bailey, L. G.: Diagnostic Value of Sodium Fluorescein in Epidemic Cerebrospinal Meningitis, Am. J. Dis. Child. **40**:493 (Sept.) 1930. Jerrell, O.: Brit. M. J. **1**:210, 1925.

quotient" for bromide is low.[17] In this condition one might logically expect an increased passage of various substances into the fluid because of the proliferation of blood vessels in the inflammatory process, and it is under these circumstances that the various tests are most frankly positive. In conditions in which changes in permeability may be less marked we have no other criterion with which to check the information obtained from the passage of substances in more or less than normal amounts into the cerebrospinal fluid. Many workers[18] have found decreased permeability in the majority of schizophrenic patients. It is difficult to account for such a finding on any basis of change in absorption, excretion or binding by blood or by tissues. While a widely varying blood concentration may result in varying quotients, the constancy of the quotient obtained by Walter's method in large groups of normal persons suggests that under ordinary conditions variations due to this cause do not introduce a serious error. In any discussion of meningeal permeability one must speak in terms of the only criteria that are available at the present time.

Our results may be summarized as follows: In a study of the hemato-encephalic barrier, using eight dogs with Eck fistulas, two with complete obstructive jaundice and thirty-seven normal controls, in which meningeal permeability was studied by dyes, Walter's bromide method and the determination of cerebrospinal fluid phosphorus, no evidence of a change in barrier function was elicited. We have made our studies on dogs with Eck fistulas from fourteen to one hundred and eighty days postoperatively, in order to observe both acute and chronic changes. While we obtained traces of neutral red and of bromsulphthalein and a questionable trace of potassium iodide in normal dogs, none of these substances came through in dogs with Eck fistulas. The normal range of permeability quotients according to the bromide method of Walter is greater in normal dogs than is reported in human beings, and the quotients are higher, but all values for animals with injury of the liver fall within this range, and the average values for the control and the liver damage series are almost identical. In the summary of values for inorganic phosphorus in the cerebrospinal fluid, the average for the six dogs with Eck fistulas was 0.2 mg. per hundred cubic centimeters higher than the average for the thirteen normal dogs, and the maximum value for dogs with Eck fistulas was 0.2 mg. higher than that of the maximum value for normal dogs; two of the dogs with Eck fistulas showed higher

17. Kroll, M., and Fedoroff, H.: Ztschr. f. d. ges. Neurol. u. Psychiat. **122**:667, 1929.

18. von Rohden, F.: Arch. f. Psychiat. **87**:797, 1929. Malamud, W.; Fuchs, D. M., and Malamud, N.: Barrier Between Blood and Cerebrospinal Fluid: Changes in Permeability in Mental Diseases, Arch. Neurol. & Psychiat. **20**:780 (Oct.) 1928.

TABLE 2.—*Determinations by Walter's Bromide Method*

Dog	Weight in Kg.	Post-operative Day	Days of NaBr Before Test	Permeability Quotient	Comment
Control 1	23.6	...	5	3.9	
2	10.0	...	5	3.9	
3	11.4	...	5	4.5	
4	8.2	...	5	4.4	
5	18.6	...	5	4.7	
6	12.3	...	4	4.1	
			4	4.1	2 weeks after first test
7	10.9	...	4	4.2	
8	14.1	...	5	4.5	
9	9.1	...	4	3.8	
10	23.2	...	6	4.6	
11	20.0	...	6	4.3	
			10	3.9	4 days after first test
12	17.7	...	6	4.5	
			10	4.0	4 days after first test
13	11.8	...	2	4.0	
			7	4.3	5 days after first test
			4	4.7	9 days after first test
14	9.1	...	2	4.7	
			7	4.8	5 days after first test
15	8.2	...	8	3.6	
16	8.2	...	8	4.2	
17	15.4	...	4	4.5	
Eck 29	10.0	104	5	3.8	
		118	5	4.3	
Eck 33	11.8	22	6	3.9	
Eck 34	17.7	14	4	4.9	Same as control 12
Eck 35	20.0	14	4	4.4	Same as control 11
Eck 36	8.8	23	6	4.5	Same as control 14
Eck 37	7.9	23	6	4.9	Same as control 15
J 15	9.1	65	4	4.2	Complete obstructive jaundice
J 16	7.2	19	6	4.5	Complete obstructive jaundice

Permeability quotient of controls: average, 4.27; maximum, 4.8; minimum, 3.6. Permeability quotient of liver damage series: average, 4.37; maximum, 4.9; minimum, 3.8. Permeability quotient of Eck series alone: average, 4.38; maximum, 4.9; minimum, 3.8.

TABLE 3.—*Inorganic Phosphorus of Blood Serum and Cerebrospinal Fluid*

Dog	Post-operative Days	Number Hours Fasting	Serum Inorganic Phosphorus, Mg. per 100 Cc.	C. S. F. Inorganic Phosphorus, Mg. per 100 Cc.	Comment
Control 1	..	18	7.0	1.5	
2	..	18	3.9	1.6	
3	..	18	8.6	1.3	
4	..	18	5.0	1.3	
5	..	18	5.2	1.7	
6	..	18	6.2	1.6	
7	..	60	5.5	1.7	
8	..	60	4.2	1.5	
9	..	72	3.8	1.5	
10	..	36	6.6	1.9	
11	..	48	4.4	1.6	
12	..	48	3.8	1.8	
13	..	48	5.5	1.7	
Eck 33	49	36	5.2	2.0	
29	180	60	4.3	1.6	
34	24	72	5.3	2.1	
35	28	36	5.7	1.6	
36	24	72	6.6	1.6	Same as control 13
37	24	72	5.3	1.7	Same as control 11
Average of controls			5.4	1.6	
Control maximum			7.0	1.9	
minimum			3.8	1.3	
Average of Eck dogs			5.4	1.8	
Eck maximum			6.6	2.1	
minimum			4.3	1.6	

values than those obtained for any normal dog. It is conceivable that a much larger series subjected to statistical treatment might show results of some significance. Normal values for phosphorus in the cerebrospinal fluid are too variable, however, to allow us to attach any significance to these minor variations in a small series. We see two possible reasons for our failure to confirm the results of Lewantovsky.[9] If his control series was small, he may have failed to observe the normal variation in permeability that was indicated by our results when Walter's bromide method was used (table 2). Another factor may be that he studied all of his animals within ten days of the operation, while we made no determinations until the fourteenth postoperative day; it is not improbable that a temporary change in permeability might result simply from anesthesia and from operative intervention.

It need hardly be pointed out that these results in no way vitiate the evidence pointing to a relationship between hepatic damage and disease of the central nervous system; this evidence, clinical and experimental, has been discussed in the introduction. Our findings merely indicate that one particular line of attack on the basis of this relationship is barren of results.

Other facts that have grown out of this study are that the permeability quotient as determined by the bromide method is more variable in normal dogs than in normal human beings, and that with dogs the permeability quotient is the same within the limits of error, whether the bromide is administered for two, four, five, six, seven, eight or ten days.

SUMMARY

The hemato-encephalic barrier has been studied in thirty-seven normal dogs, eight dogs with Eck fistulas and two with complete obstructive jaundice. The methods used were the appearance of dyes in the cerebrospinal fluid, Walter's bromide method and the inorganic phosphorus of the fluid. No evidence of a change in barrier function in the presence of liver damage was found. The permeability quotient for bromide is higher and more variable in normal dogs than in normal men. Varying the duration of bromide feeding from two to ten days did not have any apparent effect on the quotient.

SPECIAL ARTICLE

CHARLES KARSNER MILLS

MEMORIAL MEETING OF THE PHILADELPHIA NEUROLOGICAL SOCIETY

CHARLES H. FRAZIER, M.D.

WILLIAM G. SPILLER, M.D.

CHARLES W. BURR, M.D.

JAMES W. McCONNELL, M.D.

AND

WILLIAMS B. CADWALADER, M.D.

PHILADELPHIA

DR. MILLS' INTEREST IN NEUROSURGERY

DR. FRAZIER

It is well within the compass of the truth to speak of Dr. Charles K. Mills, in this assemblage of his activities, as the inspiration of the Neurosurgical Clinic at the Hospital of the University of Pennsylvania. And without exaggeration one might say further that had it not been for his enthusiasm and encouragement, the inauguration of the clinic as a unit might have been deferred for many years. With his vision he foresaw what might be accomplished were a clinic established devoted exclusively to the surgery of cerebral lesions.

As for my association with the clinic at the time of its inauguration, I seemed to have no alternative; I was drafted by Dr. Mills for the service.

Chronologically speaking, the first operation for tumor of the brain, witnessed by Dr. Mills, was performed by Dr. R. F. Weir in New York on Nov. 17, 1887, and one month later, on Dec. 15, 1887, he attended the second operation at St. Mary's Hospital, Philadelphia, at which Dr. W. W. Keen is reported to have removed a large fibroma from the parietal region.

Papers read at the Regular Meeting of the Philadelphia Neurological Society, March 18, 1932. A paper was to have been read by Dr. James Hendrie Lloyd on Dr. Mills' association with the Philadelphia Neurological Society which he founded, and the Nervous Wards of the Philadelphia General Hospital which he also founded. Dr. Lloyd, however, died four days before the meeting. A paper by Dr. T. H. Weisenburg on the relationship of Dr. Mills to the American Neurological Association was also read.

To establish a diagnosis and localize the tumor, afterward exposed at operation, was an event of some consequence in those days. Possibly the first case in his own practice was one in which it is recorded, as though some moral support were needed, that Drs. S. Weir Mitchell, W. W. Keen, Wharton Sinkler and James Hendrie Lloyd were called in consultation.[1] That was in 1891. Later, a small tumor was removed by W. W. Keen, assisted by Roswell Park, whom Keen asked to trephine the skull so that "his hands should not be unsteadied by muscular fatigue." It is difficult from the description to identify the tumor, but one might conjecture a fibroblastoma in miniature, its position being sagittal, the overlying bone thickened and the origin from the arachnoid villi.

As illustrating how operations in the early days were deferred until the terminal stages, I might cite a case[2] which, as recorded by Mills, showed at autopsy an extensive gliomatosis of the cerebellum, pons and medulla oblongata. The tumor had decompressed itself through the skull to the left of the occipital protuberance, and because of its pulsation the surgeon mistook the tumor for an aneurysm and ligated the vertebral artery, obviously without effect.

At the beginning of this century, at the twenty-sixth annual meeting of the American Neurological Association, Mills narrated his experience with a patient in whom eventually he accurately localized a tumor of the superior parietal convolution. As in those days hysteria and syphilis were considered possible alternatives, the usual course of mercury and iodides was prescribed. In fact, Mills said that it cannot be too strongly emphasized that a large majority of patients with tumor of the brain suffer sooner or later from hysteria. A tumor, measuring 4.5 by 5.5 cm., was removed, and Dr. Spiller, the arbiter in all matters concerning neuropathology, described it as a perithelioma or as an endothelioma. This was a great occasion. It was the first verified endothelioma or, as it is now called, fibroblastoma in Mills' experience, accurately localized and removed in toto. Hitherto his experience with tumors was chiefly when they were exposed at autopsy. These recent experiences of tumors exposed in vivo and removed must have been the foundation from which he visualized the possibilities of neurosurgery. To me the interesting feature of this contribution was Mills' reflections on the problems of localization. He was never more at home or more in his element than when discussing cerebral localization, a subject to which he made so many original contributions.

How well I can recall Mills standing by the operating table and directing the use of the electrode. He was tremendously interested,

1. Mills, C. K.: Am. J. M. Sc., December, 1891.

2. Mills, C. K.: J. Nerv. & Ment. Dis., August, 1892.

early in the first decade of the century, in the exact location of the motor cortex. It was his belief that the motor cortex was altogether cephalad to the rolandic fissure. At the time that he published his paper, "The Motor Area of the Human Cerebrum, Its Position and Subdivisions with Some Discussion of the Surgery of the Area,"[3] he had made 138 observations in 25 cases. Mills was especially interested in those days in establishing the fact, not then proved, that there were no motor centers behind the rolandic fissure. He drilled us in a special technic for using the electrode at exploratory operations. When the motor cortex was exposed with the aid of the electrode, he first established the main subdivisions of the motor zone: (1) for the face, (2) for the eyes and head, (3) for the arm, (4) for the trunk and (5) for the leg, and then made some precise observations as to the exact site of the individual centers. From observations made in 1 case he localized for the first time the centers for the mouth, the eyelids and the jaw.

Because of this intense interest in the motor zone he laid great emphasis on craniometric methods for determining the location of the rolandic fissure and after drilling me in a series of observations on the cadaver he adopted the so-called Anderson-Makins method. It was extraordinarily accurate.

Mills was in his sixties (1900-1910) during, shall I call it, the embryonic stage of neurosurgery? To be sure, occasional explorations for tumors had been made in the decade immediately preceding, but the foundations for neurosurgery as a specialty were being laid in the first decade of this century, and Mills was one of the most enthusiastic witnesses and contributors. He wrote:

> Neurologists and surgeons, stimulated on the one hand by the development of both cerebral and spinal localization, and on the other by improved methods of surgical procedure, took up the question of the localization of such lesions and their removal with enthusiasm. After a few years a lull of interest occurred, the result of various causes; but during the last ten years this interest has been reawakened and increased, chiefly because of our advance in knowledge regarding the functions of the brain and spinal cord and the greater success which has attended operations.[4]

Then he went on to describe the successful removal of an endothelioma of the spinal cord and an exploratory laminectomy exposing what was regarded as an example of an intradural spinal cyst, "meningitis serosa circumscripta," so-called. Curiously enough, I do not remember having uncovered a similar lesion since that time. This lesion, for the relief of which Horsley had operated no less than 21 times, seems to have almost disappeared within another generation.

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3. Mills, C. K.: Univ. Penn. M. Bull. **18**:134 (July-Aug.) 1905-1906.

4. Mills, C. K.: J. Nerv. & Ment. Dis., 1910, vol. 37, no. 9.

Perhaps the historian might be pardoned were he to headline a section of his biography on "Mills the Surgeon." In one of his contributions, "The Surgery of Brain Tumors from the Point of View of the Neurologist with Notes on a Recent Case,"[5] Mills said, by way of apology for his pronouncements on surgical topics, "it is possible that I may be called to account for discussing a subject most of which properly belongs to the surgeon. . . . The development of an art is advanced not only by the work of the artist, but by the observations and criticisms of those who have a deep concern or interest in his productions." And with this introduction he proceeded to recount some of the reasons for surgical failures. He liked to map out on the scalp the cranial area to be exposed after he had localized the tumor, and at that time in a series of 22 cases his localization was correct in 20. He had outlined 6 cranial areas for osteoplastic resections which he said corresponded to regions with definite syndromes. He decried the chisel and mallet for resections as a cause of concussion and extravagant as to time. He advocated the two-stage operation under certain conditions, and temporary compression of the carotid arteries for the control of hemorrhage.

He was misled into believing that the "importance of the roentgen ray in locating brain tumors was becoming more and more apparent." At that time roentgenologists were straining their eyes to see shadows to which false interpretations were given.

How little there is new in the world. Only recently, a transtentorial approach has been proposed as a ready means of reaching angle tumors. Even in 1902, according to Mills, Keen said that when a tumor was situated in the under surface of the cerebellum and laterally to the pons, it could be reached only by elevating the temporal lobe and incising the tentorium behind and parallel to the ridge of the petrous bone! Mills recognized the difficulties at that time attending the exposure and removal of cerebellar tumors, and with justification. The cerebellar technic of today had not been developed.

The technic of those days disturbed Dr. Mills not a little. In the clumsiness of its making and in the limitations of the bone flap he realized serious technical defects and handicaps. He wrote then, "I am convinced by my obser[illegible] this and in other operations for the removal of brain tumors, a[illegible]s of the utmost importance that some speedier method of opening the skull . . . be employed."

It was with a sense of pride in the early days of the Neurosurgical Clinic that Mills collected the papers of two symposia and distributed them in bound form. That on "Tumors of the Cerebellum" appeared in 1905 and contained papers by Mills himself, de Schweinitz, Weisen-

5. Mills, C. K.: Philadelphia M. J. **10**:836 (Nov. 29) 1902.

burg, Ludholz and myself. The second volume, entitled "Tumors of the Cerebrum," appeared in 1906 and contained contributions from Mills, de Schweinitz, Spiller, Weisenburg and myself.

It might not be without interest as a matter of record in this memorial of Dr. Mills' activities to append a list of the first cases that he referred to the Neurosurgical Clinic. Mentioned chronologically, they were as follows:

Nov. 16, 1902: The first patient with major trigeminal neuralgia, for section of the sensory root.

Dec. 7, 1903: A patient from whom "a sarcoma" of the cerebellum was removed. The patient survived the operation four years.

Oct. 12, 1903: A patient with a cerebellar syndrome. The lesion proved to be a pseudotumor, the first of our series, and the patient was alive and well in September, 1931.

Sept. 21, 1903: A patient from whom was removed what at that time was recorded as a "sarcoma" of the parieto-occipital region. This was the first cerebral tumor of Mills' series in the Neurosurgical Clinic.

March 14, 1905: The first patient with a lesion of the spinal cord, which proved to be a circumscribed serous meningitis.

Sept. 19, 1908: A patient with persistent tinnitus and vertigo for the relief of which Dr. Mills advised section of the auditory nerve.

July 18, 1912: The first case of our pituitary series, classified as a "pharyngeal duct cyst," and a year later the first case of tumor of the pituitary body, recorded as an adenocarcinoma.

After a lapse of thirty years my memory fails, I am afraid, in an attempt to do full justice to the many ways in which Mills stimulated the development of the Neurosurgical Clinic. Naturally, his thoughts were directed in channels that had more to do with diagnosis and localization than with the details of surgical procedure. But his mind was always resourceful. His proposal for section of the auditory nerve in conditions simulating Ménière's disease preceded by twenty years a practice that was recently introduced by others as an original conception. In 1912, under his direction, I performed intradurally an anastomosis of the first lumbar to the third and fourth sacral nerves for loss of bladder function after spinal trauma, an operation that proved beneficial to the patient in this instance. But curiously enough, this method of relief for otherwise hopeless cases, though physiologically sound, has never since been adopted.

These are but two illustrations of his ingenuity and initiative. There were many others.

It is assigned to another speaker to speak of Mills, the man. I could ill fulfil the task myself. But I shall always think of his gentle spirit, his kindliness and his unselfishness. I shall not forget his stimulating influence. And with these Christian traits there was the master intellect, big enough and broad enough to grasp and penetrate the intricate processes of the human mind.

DR. MILLS AS A NEUROLOGIST

DR. SPILLER

Three men during many years have been to us representatives of those who founded the Philadelphia Neurological Society, and all have passed away within one year. Their names lent dignity to the proceedings of the society, and their loss is irreparable. We have met here to honor Dr. Mills, but we cannot forget Dr. Dercum and Dr. Lloyd.

It is difficult to describe Dr. Mills in any facet of his many-sided personality. One realizes his own inadequacy to perform this task, and longs for the power that Dr. Mills would have shown were he living and placed in similar circumstances.

I have recently reread his presidential address at the fiftieth anniversary meeting of the American Neurological Association. Could any other man have written a paper like this, covering a period of fifty years and containing personal reminiscences of many of the members of the association? Throughout its length one detects the kindly nature of the speaker and his extensive knowledge. No wonder he was hailed as the dean of American neurologists. Dr. Mills kept scrapbooks in which he collected through many years a record of events in which he was interested. I recall his delivery of this address, long, but never tiresome, and given without the aid of notes by means of his remarkable memory, which he had cultivated through the necessity of listening to articles read to him.

The limited time at my disposal prevents an exhaustive review of his accomplishments and work, but fortunately these are on record in the "Encyclopedia of Pennsylvania Biography," edited by John W. Jordan, L.L.D.; in the testimonial published in Old Penn at the time of his retirement from the chair of neurology at the University of Pennsylvania; in the testimonial published by his lifelong friend, Lloyd, in Old Penn and in his address at the dedication of a tablet in honor of Dr. Mills in the Philadelphia General Hospital, and in the obituaries by Weisenburg and Jelliffe. I prefer to speak more of my personal knowledge of the man.

His bibliography, published in the anniversary volume of the American Neurological Association, terminates with the year 1923, but through the kindness of his daughter, Mrs. Weisenburg, I have had access to the continuation of the unpublished list of his papers. In every year from 1923 to 1931 he produced one or more papers, and Dr. Mills was in his eighty-sixth year when he left us.

It is well to picture so far as possible the condition of neurology in this country at the time when Dr. Mills began his work. The chief interest was in the clinical manifestations of disease of the nervous system and in the gross appearance of the brain. The relation of disease

to the microscopic anatomy and microscopic pathology of the nervous system was not an object of serious study. Neurologic disorders were not attractive to many, and Dr. Mills has told me that in his attempt to establish neurologic wards at the Philadelphia General Hospital he accepted cases of old hemiplegia and similar conditions which many physicians were glad to have removed from their services. S. Weir Mitchell had become distinguished for his clinical neurologic work.

Dr. Mills' first paper, written in 1872 and the only one recorded until 1875, was on spectrum analysis, not a neurologic subject. His first neurologic paper was "Clinical Notes on Forty Cases of Chorea," in 1875, and at this early date he showed his inclination toward neurology, although he wrote on other subjects also. In 1876 and 1877, it is evident that he was interested in electricity, and his papers from this period show that the disorders of the nervous system had become his chief interest. The titles of his early papers indicate chiefly clinical conditions, but in 1879 he wrote one on tumor of the brain and one on localization of diseases of the brain. Thus early he manifested his interest in cerebral localization. It was in about 1881 that he turned his attention also to mental conditions in a paper on hypnotism, and this was quickly followed by several papers on the brains of criminals, inspired partly by the case of Guiteau and others, showing his increasing interest in mental diseases. The study of the gross morphology of the brain's surface appealed especially to him, and he chose this subject for his presidential address before the American Neurological Association in 1886; he was associated in this paper with Andrew J. Parker. His association with John B. Deaver and W. W. Keen, as shown by his titles, began about 1890, but it is well known that Deaver did not prefer the surgery of the nervous system, although the association with Keen continued through many years. An important contribution to localization of the acoustic cortical center for words as well as sounds was published in 1891, and the brain described in this study is still in the laboratory of neuropathology of the university. The first important reference to aphasia is found under the date of 1891, and this subject always retained its appeal for him. He contributed valuable articles on neurologic subjects to many systems of medicine. Legal medicine early claimed his attention and he taught it at the University of Pennsylvania. He was among the first to advocate the theory of the separate localization of movement and sensation in the cerebral cortex.

My first association as joint contributor with him was in 1896, and from that time I saw much of him. With his appointment as clinical professor of nervous diseases in the University of Pennsylvania in 1901, changed to professor of neurology in 1903, his papers became more definitely devoted to neurologic subjects, and always localization maintained its importance in his mind. On examining the titles of

his papers one is amazed at the wide field of his interests. His bibliography is longer than any of those recorded in the fiftieth anniversary volume of the American Neurological Association, and he added to it until the year of his death. In 1924 he received the signal honor, never previously given to any one, of being elected a second time as president of the American Neurological Association on its fiftieth anniversary. Since then this honor has been bestowed on two others. He was reappointed president because he was unanimously recognized as the one best deserving the honor and as the oldest living American neurologist. He was greatly interested in developing graduate neurologic teaching in Philadelphia.

My association with him in the Department of Neurology in the University of Pennsylvania, which was entirely in accordance with his own wishes, brought us in close contact. To both of us the prestige of the department was the great object in life. For many years my office was near his, and it was my custom every few days to drop in for a chat with him after office hours. A frequent salutation was "What's new?" His mind was ever alert to what was going on in neurology, and he spoke freely to me concerning medical men and medical matters. There was nothing of pettiness in Dr. Mills. He stood for all that was best, and delighted to give honor where honor was due. He resigned the chair of neurology in 1915. He received many honors from foreign neurologic societies, and recognition by his neurologic colleagues of his own country was unstinted. He wrote one volume of a textbook on neurology which was prepared with the same care that he gave to all his writings, but an intended second volume never appeared. This work was left unfinished in the same manner as were the two volumes on the anatomy of the brain by the Dejerines. It was typical of Dr. Mills, when he was engaged in any study, to digest the literature of his subject, and his papers never indicated hasty preparation. His interest in neurologic problems was so great that sometimes he found it difficult to dismiss them in order to see his patients, and his duties at the University of Pennsylvania when he was in charge were never pushed into a subordinate place. He was deeply interested in Bárány's work, reported at the International Medical Congress in 1913; on his return to Philadelphia, with characteristic zeal, he inspired Isaac Jones to put these methods into use, and he had much to do with the book published by the latter.

His last public appearance was at the Philadelphia Neurological Society a few days before he passed away, and he never lost his interest in this society. As he left the meeting that evening, before it was over, I stepped out to greet him in the hall. He was always pleased by the attention of his friends. He spoke then of his intention to attend the meeting of the American Neurological Association in Boston and did not consider the trip a serious undertaking. He always looked forward

to the annual meeting of this association as one of the greatest events of the year. He attended the dinners and was always expected to make a speech. His enthusiasm was unbounded. I frequently said to him that he was younger in spirit than some men from ten to fifteen years his junior. He was loyal to his friends; no man was ever more so. Among those who had passed on and whom he honored with his pen were S. Weir Mitchell, Alfred Reginald Allen, James Jackson Putnam, Horatio C. Wood and Edward Mercur Williams. His place in neurology is assured.

DR. MILLS AS A TEACHER OF MENTAL DISEASES

DR. BURR

It is impossible to get a correct idea of the personality of a man cut up into bits, with each piece studied as a thing apart. It is better for the reader to have the whole man studied by different men. Your committee, however, felt that it would be wiser to have Mills studied by several men, looking at him from different angles, especially since all the speakers knew him well and all would, no matter how much they tried to keep strictly to their texts, break into each other's pastures, and present the whole man as they saw him and not a mere bit of him.

Mills came into psychiatry through the gateway of neurology. Like most men of his generation, his interest in the scientific side of medicine arose out of his earlier interest in what was then called natural history, now biology, and in the future will be a part of biophysics. In his early manhood, and for years thereafter, the influence of Darwin and his interpreters, Huxley along one line, Herbert Spencer along another, was predominant. Hughlings Jackson influenced him greatly in his medical work. Cerebral localization was making rapid strides and physiologic psychology, as studied especially by Wundt, ruled in the scientific world. Mills was taught, and unconsciously absorbed, the idea that to get at truth one must study facts, or things or actions and then, with the data assembled, draw conclusions. He was trained in the method of that great mind, Bacon. That method still is used exclusively by biologists and physicists, but not a few psychiatrists, and a few psychologists who have not been trained in laboratory methods or, being emotional rather than rational, have thrown them aside and reverted to the older method, which flourished before Aristotle. Their method is to evolve a theory of the nature of mind, study people for evidence of its correctness and then use, as the test of its accuracy, the question, does it work, i. e., explain things? If it does, they are satisfied that they have solved the problem. Mills was not in sympathy with this method.

He was appointed lecturer on mental diseases in the Medical School of the University of Pennsylvania in 1877, the same year in which he

founded the nervous wards in the Philadelphia Hospital (Blockley). In 1893 he was promoted to the professorship of mental diseases, which he held until I succeeded him in 1901, he then becoming clinical professor of nervous diseases, and in 1903 professor of neurology. He was greatly influenced in his early medical life by Dr. Isaac Ray. Ray was appointed "lecturer on insanity" at Jefferson Medical College in 1870, and Dr. Richardson gave clinical demonstrations of the different types of mental diseases to medical students at Blockley. Mills stated that Ray and Richardson gave the first instruction on mental diseases in the Philadelphia medical schools and hospital, after the early lectures of Rush and possibly of Dr. Robert K. Smith. I think, though Mills was too modest ever even to intimate it, that his lectures were the first really serious and systematic attempt to teach the science and art of psychiatry in modern times in Philadelphia. Ray is best remembered for his great work on the "Jurisprudence of Insanity." The earliest consultants in the department for mental diseases of the Philadelphia Hospital were Drs. S. Weir Mitchell, Horatio C. Wood and Charles K. Mills. They were appointed in 1884, or about that time. Mitchell hoped to make this department a great hospital and school for mental medicine. He failed in making the guardians of the poor see the light, and resigned. The study of organic neurology was very active in Mills' life. Flechsig traced the tracts in the cord and brain, Ferrier was a tower of strength, Horsley and others started cerebral and spinal surgery and Wundt and others did great work in physiologic psychology, but psychiatry was, as it still remains, the most backward of the sciences underlying medicine. As an art, it had made one great step before Mills was born. Late in the eighteenth century, Dr. Pinel, in France, and the Quaker, Tuke, in England, had humanized treatment, but they were more interested in helping the sick than in finding scientific truth. In Mills' time, students were still trying to classify mental disorders by symptoms. People in general still regarded insanity as a visitation of an angry god, a punishment for sin either of the victim or of his forebears, a mysterious thing not controlled by natural law and of which families were ashamed. The discovery that cretinism was caused by disease or abnormal development of the thyroid gland, and that feeding the patient with thyroid sometimes had marvelous curative results was the first step in discovering the relation of the so-called ductless glands to mental function as well as to physical growth.

I first met and became slightly acquainted with Mills when I was a medical student at Pennsylvania, from September, 1883, to May, 1886. He gave a course of clinical lectures, and occasionally took a group of students to visit the wards of the State Hospital at Norristown. Attendance at his lectures was entirely voluntary. Students neither acquired official merit by attending nor lost credit by remaining away. In those

days, neither state, law nor university statutes required a student to know anything about psychiatry in order to get a medical degree or license to practice. I am not sure, but my recollection is that registration of practitioners in Pennsylvania became a legal requirement some time after my graduation. Examination by state boards was instituted still later. But notwithstanding the fact that Mills' course was entirely voluntary, the more intellectually inclined students attended faithfully. I, of course, was, or classified myself, among the very intellectual, and took every opportunity to learn all I could about diseases of the mind. Looking back at my young self from the stage of the youth of old age, I know that my opinion of myself was to say the least a little flattering. I was far from being intellectual, was very crude and very undeveloped and had all my battles learning how to reason before me. But of course, with the dogmatism of youth I instantly formed an opinion about Mills. One thing struck all of us: his intellectual honesty. As I have written elsewhere, he did not use his position for purposes of advertising. He did not seek the acquaintance of the student sons of rich or important people. He was in the best sense a simple-minded man. Medicine to him was not a trade but a much loved work and hobby. He, on the other hand, was not at that time (remember it was almost fifty years ago) an inspiring teacher, nor was he a lucid speaker. He did not give a logical and systematic course, but lectured on any subject that interested him at the time. I speak of this because I like to compare him, as he then appeared, with what he became later. Always, he had intellectual curiosity and was one of those rare men who, giving no promise of genius in early life, continue to develop years after the average man, or even the talented man, ceases to grow, becomes crystallized or even mentally shriveled. Mills became a better and better teacher as the years passed. More than this, his intellectual field widened and he became more philosophic minded.

Midvictorian prudishness, as the twentieth century calls it, still held sway during the time that Mills taught psychiatry, and he was reticent about discussing sex and careful not to present before the class patients who might shock the modesty of ingenuous youth. Really, we were neither as innocent nor as ingenuous as it was the custom of the time to assume. Since then, things have changed mightily. Sex has become a matter of dinner table talk, and one school of psychiatrists teaches that "libido" is at the bottom of all mental ills; that it not alone absorbs the whole of conscious life but pursues us into the hypothetic subconscious, breaks through in our dreams, and that any elongated object seen in a dream symbolizes an important organ and proves that we are all, all the time, subconsciously thinking about something that we are not thinking about at all. Mills was antipathetic to this school of psychiatry. But then, as these gentlemen, and sometimes ladies, say, he was merely a

student of the organic, knew nothing about soul stuff and could not attain to the dizzy heights of sexual metaphysics.

He wrote extensively on mental diseases and drug habits, on nursing the mentally ill and on hypnotism. I shall not bore you with the long list of titles. He at one time taught medical jurisprudence at the University of Pennsylvania and wrote in explanation and criticism of the legalistic attitude concerning mental functions. He tried, as many others have done, to explain how in a world ruled by natural law there can be freedom of will. He showed the illogicality of the legalistic conception of responsibility. He appeared in court many times as an expert, and judges and juries held his intellectual honesty in high esteem. His opinion could not be bought. He was one of the many men who have proved the fallacy of the cynical saying that "every man has his price."

Mills' great work, as a psychiatrist, was not as a discoverer or investigator but as a teacher, almost unconsciously and by example, not by preaching, of the great fundamental thing that knowledge can come only by clear thinking based on accurate perceiving. He gathered his facts and then drew conclusions, careless and unconcerned whither those conclusions might lead. Also he was very human, quiet but just in judgment of his students, and helped all young men who came under his influence who were worth helping. Rarely did he mistake geese for swans. He continued to grow in knowledge and in wisdom till death, and, if there be, in truth, as certain old Jewish scholars thought and taught, an Academy on High for those worthy of admission, he will be a student there.

PERSONAL ASSOCIATIONS WITH DR. MILLS

DR. MCCONNELL

I shall present some remarks on my personal associations with Dr. Charles K. Mills, and in doing so my intention is to forget the strictly professional side and relate incidents that will construct pictures of certain phases of the man's make-up which could be drawn only by one who, like myself, had almost a life-long intimate acquaintance with him.

My earliest recollection of Dr. Mills dates back many years when, as a small boy, I had the happiness of greeting him and his bride who were paying a visit to the house of my father. Despite my extreme youth, I was so taken with the kindliness of his manner and his persuasive friendliness that my uncle doctor, for such he was, became then and ever remained the ideal of everything that I wished to be in the future. My education was in large part influenced by suggestions from him and the recommendation by him of his Alma Mater eventually led me to the same medical school where I prepared for my professional career. He chose the hospital where I acted as resident following my graduation, and on the completion of my service in that institution he

received me in his office where he endeavored to inculcate some of the virtues possessed by him, many of which I was unable to absorb.

Almost immediately I was conscious of the tremendous interest that this big man had in those who were attempting the rather precarious existence of the young physician, and now, in retrospect, I can visualize many who appeared in his service or whose lives were distinctly influenced by him. In his office at the time I went to him was Dr. M. Imogene Bassett, who had for a long period been his associate and who left him to take up the practice of her profession in Cooperstown, N. Y., where at the present time a magnificent hospital is dedicated to her memory. Among others were J. Ramsey Hunt of New York, Thomas Orbison and Isaac Jones of California, Andrew Woods and Edward Mercur Williams of Iowa, Edward Stevens of Colorado, John Outland of Kansas and Carl Camp of Michigan; not forgetting the dozens in and about Philadelphia, including such names as Potts, Spiller, Frazier, Weisenburg, Joseph Sailer, Elizabeth Bundy, Reginald Allen, Ludlum, Edwin S. Saylor, Bunting, George Wilson, Temple Fay and others. Indeed, Dr. Mills' great interest, outside of his efforts in the advancement of science, seemed to be an inordinate desire to help the younger physician, and he never failed to take advantage of an opportunity to do this. Did he find a man more interested in surgery or internal medicine than in neurology, he would go out of his way to be of some definite professional help, and today there are many surgeons and physicians who proudly attribute much of their financial and scientific success to the urgings of Dr. Mills.

As my life became completely entwined with his I began to appreciate his idealistic qualities, and with the advance of years he became to me more than ever the paragon of all the virtues. The days I lived in his household were hours of great happiness. They were helpful in a professional way, and meal times were feasts of reason as he disseminated the broad knowledge possessed by him to those about the table in conversations that always were informative and tremendously interesting.

He concerned himself keenly about his family; the play of the small children and their education as they became older he regarded as matters of great moment. He had joy in their successes, and their failures afforded him the opportunity for the administration of stimulating advice. One of his children was an invalid for several years, by reason of an accident at a very early age, but always and ever Dr. Mills, the physician, gave pain when occasion required and Charles K. Mills, the father, suffered intensely with the patient. For a long time the partner of his married life was a secret sorrow because of mental aberration due to cerebral arteriosclerosis. He exhibited for her the most wonderful consideration, had a guardian appointed for her after long battling

against it, and refused, contrary to the most strenuous advice, to place her in an institution, always answering arguments in the same way: "No, that's my job and I'll do it as best as I can." Business cares might be mountain high; fatigue might be extreme; desire for other things might be most attractive; always he operated as the attentive, thoughtful, kind, sympathetic husband, hoping, yet knowing the future held nothing for the wife.

Dr. Mills was afflicted from childhood with deficient eyesight, yet was able to see fairly well with lenses. In the early nineties he was knocked down by a bicycle and suffered a detachment of the retina of the right eye. Under the kind care of oculists who flocked to his aid he was courageous and uncomplaining and most thoughtful, and I remember an afternoon when he confided to me that his days of usefulness were over and that he was unable to work out any plan for the future. Thirty-five years after this tragedy, he closed a life replete with accomplishments that should make some of us possessed of the full measure of faculties ashamed of our lean efforts and our useless existences.

One trained to systematic recording would regard Dr. Mills' methods of working as unique for such a busy man, and by many they would be regarded as careless. Ordinarily, he used his marvelous memory as his principal record book, although the salient features of the history of any case, with the diagnosis and probable line of treatment, he scribbled in a small notebook made of a handsome leather case and a filler of easily detached leaves of fine white calendered paper with gilded edges. As he filled one of these his secretary stored it in a cabinet according to the date. He dictated letters from these meager notes with the added facts culled from his mental storehouse. Rarely, if ever, did he make a mistake, and his ability to recall the finest details was a source of astonishment.

I had the honor of being one of his associates in the preparation of his book, "The Nervous System and Its Diseases," and he amazed all of us by his ability entirely to concentrate his mental and physical powers in the making of this book with almost complete exclusion of affairs of any other kind while he was thus employed.

After his eyesight was so badly damaged, the use of what vision remained was restricted to the minimum, and it fell to the lot of his various secretaries, his family and his medical assistants to read to him. Frequently I spent hours transferring to his mind the contents of medical journals or of books, and he would stop me in the middle of a paragraph while he dictated to his secretary a short note of something that appealed to him in the text. It was not unusual for him to have under way, simultaneously, as many as four different pieces of literary or scientific work, and the mental gymnastics required of those who

assisted him were as nothing to him whose brain seemed to be a series of pigeon-holes from which he would remove or in which he would place the material needed or used.

Dr. Mills' study of patients was always a thorough procedure. He kept pace with the newer methods of examination; he utilized modern instruments; he always recalled the practices of his "general work" days, and he could differentiate cardiac and pulmonary conditions as well as the best chest specialists. The handicap of his blindness forced him to depend on the powers of observation possessed by his various assistants, but he never accepted their results without close questioning and a caution as to possible or probable error. When the Babinski sign became fashionable as an indication of organic nervous disease, Dr. Mills spent hours in the Philadelphia Hospital perfecting himself and his associates in the best method of eliciting the phenomenon and of interpreting it, as well as its variations. Normal and abnormal subjects were tried out until he had the whole thing perfect in his mind.

The high scientific position attained by the man never seemed to alter his original conception of the attitude of the physician toward his patient's finances. He had little or no idea of the value of his opinion calculated in dollars and cents; and many of the troublesome, serious problems of his professional career resulted most insignificantly in a monetary way. When his attention was called to things of this kind his answer most commonly was, "Well, they cannot afford to pay so much," and that decision was final. I recall his first trip to Europe, when he went as the medical companion of the wife of a well known Episcopalian bishop. He was absent from his office for many weeks, but he charged for his services much less than many present-day specialists receive in one month for work in their offices. Dr. Mills regarded the whole thing as a pleasant vacation which cost him nothing and furnished him spending money. Often he talked of the Guiteau and other famous medico-legal cases and of the remuneration that came to him from them, a return that would astonish experts nowadays who receive greater fees for attendance and testimony in ordinary murder trials.

Age did not take from this man any of the lovable qualities of his earlier life, but as contacts with his medical friends became less frequent he found greatest happiness in associating with his three sisters, the remaining members of his family. Two of them were wives of clergymen, and while Dr. Mills was not without religious belief he regarded as enthusiasts those who failed to take their religion with some of the grains of common sense salt. Arguments on matters relating to the Bible were frequent, and the debates between these wives of clergymen and the thinking medical man were delightful. Once he was preparing a paper and among the volumes consulted was the "Life of Christ" by Renan. Some days later his three sisters were entertained at luncheon

and the conversation drifted to knowledge of the Bible. He bet these excellent ladies that none of them could name the twelve apostles. They would not accept his wager. They could not name them. With great glee he immediately repeated the full list without the slightest hesitation, and then excused his guests for their failure by announcing that he had purposely memorized the list that day.

His infrequent illnesses were sources of amusement to those of us who dealt with him in a professional way. He always wished to know what his medical attendants thought about him, and he was ever ready to discuss the interpretation of symptoms, assuring us that none of us knew anything about medicine, that he was being slowly poisoned by the drugs given, or perhaps dying because medicines were not being administered. After Dr. Mills' return from Europe in 1929, he suffered from some prostatic trouble and the urologist in attendance was anathematized by the patient to the point of making him rebel and suggesting discontinuance of attention. Dr. Mills' recognition of his unfairness resulted in the establishment of a regard for this surgeon that persisted to his last days; frequently he recalled his kindness and great skill.

The ancestry of Dr. Mills in various ways offers explanation for the qualities more often observed by his friends and less familiar to his confrères, who were wont to look on him as a man of science unusually skilled in deduction and most uncanny in his correlation of histories, traits and symptoms.

His father came from England as a boy, and during his relatively short life made himself dear to family and neighbors by a kindly manner, a sympathetic ear, an understanding mind and a willing hand. A man of sensible religious trend, he never failed to appreciate the fallibility of every one and to judge accordingly. His mother, a native of the United States from below Mason and Dixon's line, possessed remarkable maternal qualities which she utilized in the rearing of a large family. She delegated some of the care and training of the younger children to the older ones while she helped to look after the sick and the dying of the neighborhood. Of rigid morality, she had little pity for the wrongdoer; austere, she never failed to punish infraction of the rules; most meticulous, she could not condone carelessness; a strict disciplinarian, she required instant obedience.

Such ancestral characteristics must certainly have influenced the development of this man into the physician who regarded the patient as a human being in distress; the teacher who strove to acquaint his students with facts rather than theories; the hospital chief who never forgave lack of interest but was willing to give oceans of time to the resident physician who showed desire to learn; the aging doctor who had thought for the neophyte in medicine; the wise counsellor who constantly kept in mind the frailty of human nature.

The death of Dr. Charles Potts was a great blow to Dr. Mills who, I believe, appreciated Potts as a neurologist more than did any other man. The dramatic death of Dr. Dercum shocked him considerably, but his reaction to it was, "Well that's a fine way to die." It was not until his life-long friend and associate on the staff of the Wagner Free Institute of Science, Dr. Henry Leffman, died soon after Dr. Dercum that Dr. Mills seemed to contemplate the nearness of the end of his own life, but dauntless, as always, he attended the meeting of the Philadelphia Neurological Society on Friday, May 22, 1931, and, as he said, he enjoyed it thoroughly. During the night of May 22 and 23 he became ill, but with his exceptional bravery he refused to stay in bed. Despite the paroxysms of coughing he continued to prepare for the journey to Boston to attend the meeting of the American Neurological Association —his greatest scientific love. On the Wednesday preceding his death, realizing that the meeting would assemble on the next morning he said to me, "Well, Bill, I guess we can go up to Boston tonight, can't we?" I answered, "No, I don't think it would be wise." His eyes filled with tears and he said, "I'm sorry, for I suppose I will not attend many more of these meetings." The hours following passed with him always the "gentleman unafraid," with relief obtained from his terrible sufferings by the administration of narcotics and with him expressing the desire not to make trouble for any one, not to be a coward. Early in the morning of his death he was stuporous, apparently in his last sleep. With a great suddenness he roused, conscious of his surroundings, and he sensed me standing beside his bed. He wished to get out of bed and stretch himself, and although I advised him against doing so, my resistance to his persuasion was not great. I put my arm around his frail body and stood him on his feet. It was but a few moments when he said to me, "I'll get back now; I guess I am tired." I lifted him into his bed and he requested that he be turned on his right side. I did this for him, and he put his right hand under his cheek and said, "Now I am comfortable and I'll take a good sleep." Almost before we could realize it he was gone without a struggle, without noise of any kind, just the passing out of this beautiful character as he would have planned it, with the American Neurological Association assembling.

THE ASSOCIATION OF DR. MILLS WITH DR. S. WEIR MITCHELL

DR. CADWALADER

To have the privilege of joining in paying tribute to the memory of Dr. Charles K. Mills is to me a great honor. I wish that it were possible for me to pay this tribute adequately by presenting a full and interesting recital of the fruits of this association of two of these masters of the

subject in which we here are so deeply concerned. There is, however, such a paucity of existing evidence that I can only place before you such facts as I myself have known and witnessed.

Dr. Charles Karsner Mills and Dr. S. Weir Mitchell, during their long careers as physicians and instructors of medicine, exercised a powerful influence on the field of neurology, not only in Philadelphia, but throughout the entire United States.

When a boy of 18, Dr. Mills served in the Union Army in the emergency campaigns of the Civil War during the years 1862 and 1863, and was present at the battle of Gettysburg. His war experiences must have made a deep impression on him, just as they do on most thinking men, and were undoubtedly among the incidents in his early life that led to his sympathetic friendship with Dr. S. Weir Mitchell in later years.

I have on more than one occasion heard these two men discuss the events of the Civil War together. Dr. Mitchell was sixteen years older than Dr. Mills, and had been a contract surgeon in the Union Army in charge of a military hospital in Turner's Lane in Philadelphia. A description of this circumstance in Dr. Mitchell's life appears in one of Dr. Mills' writings. It was out of this hospital camp that later grew the Orthopedic Hospital and Infirmary for Nervous Diseases. Dr. Mills has said:

> It was at this hospital, which was at the time opposite the buildings of the University of Pennsylvania on Ninth Street, that I got my first glimpse of Mitchell, working with his assistants on the study of patients coming to the outdoor service. Even as an undergraduate student, I was impressed by his remarkable personality and his skillful clinical methods. Mitchell continued his connection with the infirmary as attending physician and consultant until the time of his death. Here he gave many of his delightful conversational clinics and conferences, some of which I had the pleasure of attending.

Dr. Mills and Dr. Mitchell not only discussed the military events of the Civil War together, but also considered the different aspects of the effects of war injuries on the nervous system. This mutual interest in the subject appears to have been one of the influences that led Dr. Mills to specialize in neurology.

Like Dr. Mitchell, Dr. Mills had never had an opportunity in his younger years of studying, under the microscope, the pathologic anatomy of the nervous system, for this means of research did not come into use in the United States until nearly twenty years later. Being older than Dr. Mills, Dr. Mitchell was trained essentially as a clinician, but developed a profound insight into physiologic methods of investigation; he did not have the advantages that Dr. Mills possessed through his ability to study postmortem material.

Dr. Mills has said of himself: "After my appointment as neurologist to the Philadelphia Hospital, I soon had unusual opportunities to study

human brains, and the macroscopic examination of the brain soon became almost a passion with me."

In an address on S. Weir Mitchell, in 1914, Dr. Mills stated:

> When the opportunity came to me in 1877 to start a department for nervous disease in the great charity hospital of Philadelphia and numerous obstacles were thrown in my way, I received from Dr. Mitchell, whom I consulted regarding the matter, such support and encouragement that I went forward with the project. He had before me seen the great value of the neurological material which was going to waste in the Philadelphia Hospital, but had not been able to accomplish his wish to turn this material to good use. He always took great interest in the clinico-pathological studies in cerebral localization and all forms of neurological work at this hospit. .

Dr. Mills was one of the founders of the Philadelphia Neurological Society. In response to a notice issued and signed by Drs. Mills, Sinkler, Dercum and Eskridge, an initial meeting for the formation of this society was held on Dec. 15, 1883, in the Hall of the College of Physicians, then at Thirteenth and Locust Streets. Nineteen physicians were present. Dr. Mills explained that the object of the meeting was to form a society of those interested in neurology. A committee was appointed to draw up a charter. The first meeting for organization was held on Jan. 28, 1884. Dr. Mitchell was nominated for the presidency by Dr. Mills and was unanimously elected, Dr. Mills being elected a vice president. They served together for a period of five years.

In 1884, Dr. Mitchell served with Dr. H. C. Wood and Dr. Mills as consultant to the Insane Department of the Philadelphia Hospital. Dr. Mills, alluding to Dr. Mitchell, stated: "He did much in the way of pointing out the shortcomings of the institution, at the same time indicating the best methods of remedying these and of improving the condition of the unfortunate insane who, then as now, were too crowded for their comfort and scientific treatment."

A year or so later, Dr. Mitchell became interested in improving the condition of insane asylums, which he felt had not been properly managed. He asked for opinions on this point from many of his colleagues, among whom were Drs. Mills, Dercum, Osler and Sinkler—all members of this society. Later, he utilized the opinions that they had expressed, as well as those of others, as the material for an address delivered before the members of the Medico-Psychological Association. This led to marked improvement in the management of mental hospitals.

Dr. Mills took a prominent part in the movement which resulted in the organization of the Congress of American Physicians and Surgeons in 1888. Writing on the "Early Meetings and Personnel" of the American Neurological Association, Dr. Mills stated:

> . . . the reason for this Congress is a matter of great interest. Dissatisfaction was created in the American Medical Association with regard to an International Congress to be held in this country in 1887.

A program for this International Congress had been prepared and published. Dr. J. S. Billings was chosen as president and many of the committees organized. Dr. S. Weir Mitchell was made chairman and the writer (Dr. Mills) secretary of the committee on neurology. Some disgruntled politicians in the American Medical Association were successful in upsetting this program. Nearly everyone who had been included in the first published announcement resigned, including the president, Dr. Billings.

An International Congress was held in 1887, but on the whole was a failure, not having in its make-up the real representatives of Medicine at home or from abroad. As it seemed impossible at this time to improve the status of the American Medical Association, a movement was started to organize a new National Society.

The second Congress of American Physicians and Surgeons was held in Washington, D. C., in September, 1891. Dr. S. Weir Mitchell was the president, and Dr. Mills was an alternate delegate to the Executive Committee of the Congress from the American Neurological Association. They both read papers at this meeting.

Dr. Mills in the aforementioned paper alluded to the meeting of the American Neurological Association held in Philadelphia in 1909, at which time he nominated Dr. Mitchell for president. "Dr. Mitchell's nomination and election," he said, "were hailed with unanimity and he accepted the honor with evident pleasure." It so happened, however, that Dr. Mitchell was not an active member of the association, but merely an honorary member. After the election was over Dr. Hammond came to Dr. Mills and said: "Mitchell was not an active member and we had no right to elect him president." Dr. Mills then asserted: "I was in a quandary, but told Hammond to hold his tongue—but nevertheless it did not hurt occasionally to violate any constitution in an absolutely good cause. This was some time before the passage of the eighteenth amendment." I am sure that when the doctor wrote this last sentence he must have been chuckling to himself.

I first met Dr. Mills in 1900, during my second year in the University of Pennsylvania Medical School. It so happened that a member of my family was desperately ill and under the medical care of Dr. Arthur V. Meigs, who subsequently became president of the College of Physicians of Philadelphia. Dr. Meigs had called Dr. Mitchell in consultation, and Dr. Mitchell later requested that Dr. Mills also be called. When these three eminent physicians had assembled in the library of the house and were ready to express their opinions and give their advice, they sent for me to join them. I felt embarrassed in the presence of these specialists, but they kindly reassured me, telling me that I would be placed in a similar position as soon as I had become a full-fledged physician, and that I had better familiarize myself with the ethics and procedure followed by physicians when consulting together. This incident illustrates the kindly nature of Dr. Mills and Dr. Mitchell. Neither ever

missed an opportunity for interesting and encouraging medical students and the younger physicians with whom they came in contact.

In one of his essays entitled "Doctor and Patient," Dr. Mitchell said:

> I know of men who are in the habit of saying that they dislike consultations and get little good from them. As compared to those who too commonly subject people to the expense of such advisers, they are the more dangerous class. Apt enough in cases of acute disease to bring into the case someone to share responsibilities which seem grave because near at hand, they continue to treat chronic cases they do not understand because there is no crisis of pain, disability or danger to bring them to reason.

It was in this spirit that Dr. Mitchell sought the assistance and counsel of Dr. Mills. They often consulted with each other in difficult cases, and it was Dr. Mitchell, appreciating Dr. Mills' particular knowledge of cerebral localization, who saw to it that the latter was appointed as consulting neurologist to the Orthopedic Hospital and Infirmary for Nervous Diseases.

Dr. Mills was generous in transmitting his knowledge to others and in affording assistance when possible; like Weir Mitchell, he never feared that others might take advantage of what he knew or believed. He had the gift of clear concise description, possessed a strong personality and had unbounded enthusiasm—for which we have an affectionate memory.

Dr. Mills has said of Dr. Mitchell: "He was an ever present example and inspiration. Poor indeed was he in spirit who did not get something of value from contact with this master in medicine—this man among men."

In conclusion I would quote as appropriate the following aphorism, attributed to the great German poet and philosopher, Goethe: "Not what the dead have failed in, nor yet what they have suffered, but only what they have done—what they have achieved—ought to occupy the survivors. In their failings we recognize mankind; in their triumphs, we recognize their real selves."

Obituaries

M. ALLEN STARR, M.D.

1854-1932

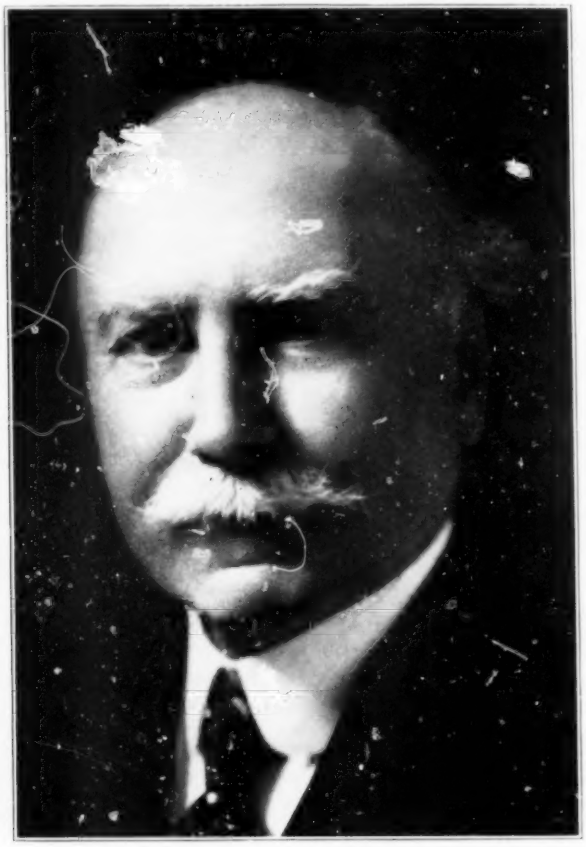
At Marienbad on Sept. 4, 1932, quietly in his sleep death came to Dr. M. Allen Starr. Thus terminated the long fruitful career of one of the pioneers of modern American neurology. He lived through the most active years of the development of neurology, and well he played his part in that development.

Dr. Starr was born in Brooklyn on May 16, 1854, and after a preliminary education in Orange, N. J., he was graduated from Princeton in 1876. In 1879, he received his M.A. from Princeton, and the M.D. degree from the College of Physicians and Surgeons in 1880. In 1884, he was awarded the Ph.D. from Columbia. Honors came later: LL.D. from Princeton in 1899 and D.Sc. from Columbia in 1904.

For all of his professional life, Dr. Starr was a neurologist. Trained by Edward C. Seguin at the old College of Physicians and Surgeons, New York, he early started to make neurology his life's work, and throughout all his active life he was a neurologist and a teacher of neurology. In 1884, four years after his graduation, he was appointed professor of nervous diseases in the New York Polyclinic Hospital Medical School. Three years later he returned to the College of Physicians and Surgeons, then the medical department of Columbia University, to begin that long devoted service to the medical school of his undergraduate days which extended over forty-five years. From 1887 to 1889, he held the post of lecturer on diseases of the mind and the nervous system. In 1889, he became professor of neurology and served as head of his department until his retirement in 1915. Until his death, he remained as professor emeritus of neurology in Columbia University. Dr. Starr to the end maintained his interest in neurology and neurologic research. He supported the research of the neurologic laboratory of Columbia and took a personal interest in what was being done.

All of the neurologic societies counted Dr. Starr among their most active members. He was admitted to the American Neurological Association in 1885, and was its president in 1897. From 1894 to 1897, he was president of the New York Neurological Society, and in 1903, vice president of the New York Academy of Medicine. For many years he was a corresponding member of the neurologic societies of London, Paris, Berlin and Vienna.

It was as a teacher that most medical men best remember Dr. Starr. In his thirty years of active teaching thousands of medical students passed under his tutelage, sat in his clinics and listened to his lectures, and none forgot him. He was at his best as a lecturer. Short, strong and active, with keen, humor-loving eyes, white haired in his later years, he was vivid and dynamic in his lectures. One felt his enthusiasm



M. ALLEN STARR, M.D.
1854-1932

as soon as he started to talk; an enthusiasm which never lagged to the end of his teaching days. Years afterward, his old students can recall cases he presented in his clinics. This same enthusiasm was seen and felt in his scientific work. It is not only the older men who remember the vigor with which Dr. Starr participated in the scientific discussions of the American Neurological Association meetings.

Dr. Starr's scientific publications covered a wide range of neurologic interest. The Semi-Centennial Volume of the American Neurological Association lists eighty articles published from 1888 to 1921. Besides this, there were his textbooks, "Familiar Forms of Nervous Disease," 1893, and "Brain Surgery," 1895. In 1897, Dr. Starr published his "Atlas of Nerve Cells" in which he brought before American medical men the then new work of Golgi and Nissl. His large textbook "Organic Nervous Diseases," first published in 1903, introduced Dr. Starr to a larger group of students. It ran through a number of editions during the next ten years.

Dr. Starr lived and worked through interesting years in the development of neurology. Starting in the old days of empiric neurology, he watched his chosen subject develop until it took its place among the medical sciences, and in that development he played a telling part. He was not a neurologist of the old school. His career may well stand as a symbol of the transition from the old to the new. He belonged to both, but primarily he was of the new.

LOUIS CASAMAJOR, M.D.

GEORGE A. MOLEEN, M.D.

1876-1932

Following a prolonged illness, Dr. George A. Moleen died at his home in Denver on June 26, 1932, from aortic and mitral regurgitation with hypertension.

Dr. Moleen was born on Nov. 16, 1876, in East St. Louis, Ill. When 6 years old he came to Denver where he received his preliminary education. A degree in pharmacy was granted to him by the University of Denver, and in 1896, the Philadelphia College of Pharmacy conferred on him the honor of a Phar.D. degree. He received his medical education at the Gross Medical College of Denver, graduating in 1900. As a medical student he demonstrated marked interest in neurology, teaching the subject at the University of Denver. Shortly after graduation he became instructor of neurology at the University of Colorado School of Medicine, where he was rapidly advanced to the full professorship, a position he held until his death. Studies in the field of neurology several times took him on trips abroad, and he was always in close contact with other teaching centers in this country.

Dr. Moleen was an outstanding physician in the Denver and Colorado medical profession. A few of the many honors conferred on him are as follows: In 1915, he was chairman of the Section of Nervous and Mental Diseases of the American Medical Association; in 1918, he was president of the Medical Society of the City and County of Denver; he was a charter member, and in 1924, president, of the Central Neuropsychiatric Association; in 1930, he was president of the Denver Clinical and Pathological Society; he was the founder, and on two occasions president, of the Colorado Neurological Society. He held membership in the American Psychiatric Association, the Association for Research in Nervous and Mental Diseases, and was most active as vice president of the Colorado State Society for Mental Hygiene. For many years he was editor of *Colorado Medicine* and played a prominent part in its development. He was elected to membership in the American Neurological Association in 1930, and at that time presented a paper, "Familial Progressive Muscular Atrophy."

The Colorado Psychopathic Hospital in Denver perhaps can be called Dr. Moleen's memorial, since he was the principal figure in its organization and an ardent supporter in its development, helping out with the building and financing of the institution. In addition to his professional prominence, Dr. Moleen was a leader in many local and civic enterprises, so his loss is felt not only by the medical profession but in the community at large.

FRANKLIN G. EBAUGH, M.D.

News and Comment

THIRTEENTH ANNUAL MEETING OF THE ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE

The thirteenth annual meeting of the Association for Research in Nervous and Mental Disease will be held at the Hotel Commodore, New York, on Wednesday and Thursday, Dec. 28 and 29, 1932. The meeting will be called to order promptly at 10 a. m. on Wednesday.

The topic for discussion at this year's meeting will be "Cortical Localization." The first session will be devoted to papers dealing with the anatomic background of localization. Dr. Bernardus Brouwer of Amsterdam, Holland, will present a general summary of the phylogeny of encephalization. Dr. Marion Hines of Baltimore will present a review of the current studies of cortical architectonics, and Dr. Frederick Tilney of New York will report on his recent studies, by the wax reconstruction method, on the comparative ontogeny of the cortex of the opossum, rat, cat and man. The second session will be devoted to physiologic topics, and will be opened by a general review of the physiologic principles underlying encephalization and localization presented by Dr. Dusser de Barenne of Yale. Dr. Harold S. Burr of Yale will discuss physiologic principles encountered in the lower vertebrae. Dr. Philip Bard of Harvard will present a summary of demonstrable differences in motor organization found in certain lower mammals, and Dr. John S. Fulton of Yale will report on motor differences occurring in the primate series. Dr. Karl S. Lashley of the University of Chicago will present the results of his studies of the visual function of the rat. The third session will deal with clinical and clinical pathologic topics. Dr. Wilder Penfield and Dr. Lyle Gage of Montreal will report on "Cerebral Localization of Epileptic Manifestations," and Dr. Joseph P. Evans of McGill University will offer some preliminary clinical studies on cases in which lobectomies have been performed. Dr. Richard Brickner of New York will report on an intensive study of a patient on whom a bilateral frontal lobectomy has been performed. Dr. N. W. Winkelman of Philadelphia will present cases indicating a correlation of trophic disturbance and retrorolandic lesions.

THOMAS K. DAVIS, M.D., Secretary.

SCIENTIFIC EXHIBIT, MILWAUKEE SESSION OF AMERICAN MEDICAL ASSOCIATION

Application blanks are now available for space in the Scientific Exhibit at the Milwaukee Session of the American Medical Association, June 12 to 16, 1933. The final date for filing such applications is Feb. 13, 1933, after which time assignments of space will be made. The Committee on Scientific Exhibit requires that all applicants fill out the regular application form. Persons desiring to receive application blanks should address a request to the Director, Scientific Exhibit, American Medical Association, 535 North Dearborn Street, Chicago.

CORRECTION

In the article by Dr. Jackson M. Thomas, entitled, "Posthemiplegic Athetosis: Report of a Case; Rôle of Corticospinal Pathways in Production of Choreiform and Athetoid Movements," in the November issue (**28**:1091, 1932), "left should be substituted for "right" in the seventh line on page 1093, making the sentence read: "Movements of these fingers were more pronounced than those of the fingers of the left hand." In the twelfth line on page 1100 "right" should be substituted for "left," making this sentence read: "The patient died of pulmonary tuberculosis, and at autopsy it was found that an old focus had destroyed the right peduncle."

Abstracts from Current Literature

THE RESULTS OF ANIMAL EXPERIMENTATION IN ACUTE INFECTIONS OF THE CENTRAL NERVOUS SYSTEM. H. PETTE, Fortschr. d. Neurol. u. Psychiat. **3**:1 (Jan.) 1931.

In the light of recent biologic and epidemiologic facts, the conception of the pathogenesis of infectious disease has undergone a change. The acute infections of the nervous system have attained pathogenic significance, by virtue of a point of view based on general biologic facts, which has advanced beyond the previously too contracted vision of neurologists.

It is only at a relatively late period that animal experimentation has gained importance in the investigation of etiologic and pathogenic problems in the realm of infectious diseases of the central nervous system. The first indications of this trend were seen in the period of investigation of neurosyphilis. The results of these investigations led to an increased fund of general, biologically interesting findings; knowledge of the pathogenesis of the metasyphilitic diseases (tabes and dementia paralytica), however, was not materially advanced by them. The inflammatory reaction of the central nervous system, originally regarded as syphilitic, when rabbits were inoculated with material from human metasyphilis, turned out to be the result of another, occasionally even an epidemic, infection (so-called spontaneous encephalitis of rabbits) on further investigation and control experiments. According to various observers it was due to a protozoid organism, the so-called Encephalitozoon cuniculi.

Plaut's method of cisternal puncture in animals, making it possible to examine the spinal fluid, offers a useful and easy means of recognizing inflammatory processes in the central nervous system, even if clinical signs are absent.

A new phase in experimental investigation began when Doerr and Levaditi held that the excitant of epidemic encephalitis is identical with that of herpes.

Symptomatology and Anatomy of Herpes Simplex.—Herpes simplex is a localized process in the epidermis of the skin and the mucous membranes which is histologically nonspecific; it appears in similar form in zoster and varicella. An isolated efflorescence may extend into the superficial layer of the stratum proprium; processes of this type, in contrast to uncomplicated herpes, heal with scar formation. The fact that herpes simplex appears occasionally in symmetrical or even in apparently segmental arrangement brought with it the coining of the term zosteriform herpes. Herpes zosteriformis is biologically in no manner different from genuine herpes simplex.

If one insists that herpes simplex is a local disease of the skin and mucous membranes, independent of areas supplied by definite nerves, a condition which usually appears in consequence of acute infectious diseases (pneumonia, epidemic meningitis, malaria, etc.) or as an accompaniment of various endocrine disturbances (processes of generation in women) as well as of acute gastro-intestinal disorders, the question still remains unanswered whether the agent causing herpes simplex is not by itself capable of causing acute febrile states (febris herpetica was first described by Griesinger). Despite various authors (Kühn, Schottmüller), there is today probably no doubt that there exist febrile states of short duration with extensive herpes eruption which cannot be interpreted as anything other than primary herpes infections. Animal experiments have supported this view. Gildemeister and Heuer have succeeded occasionally in finding herpes virus in the blood stream in experimental animals that had been inoculated on the skin.

Although clinical observation was incapable of proving the unity of all herpes eruptions, the situation suddenly changed when Grüter, in 1912, succeeded in inoculating the cornea of rabbits with the contents of herpes vesicles and then transmitting the experimentally produced herpes (in 1919) back to the eye of a

blind patient. Using Grüter's technic, Löwenstein (in 1919) showed that every herpes eruption, regardless of its origin, could be transmitted to the cornea of rabbits, and that further corneal transmissions could be made from the experimentally produced herpes. In 1920, Doerr and Vöchting first recognized that the contents of the herpes vesicle produced on the cornea of rabbits does not limit its influence to the cornea but is apt to extend to the central nervous system and cause an inflammatory process there which spreads with great regularity corneally as well as cerebrally. Proof was thereby produced of the encephalitogenic characteristics of the herpes virus.

The first clinical observation of encephalitis in the experimental animal following injection of material from the contents of a herpes vesicle into the cornea was made by Stocker (1920). It was shown that healthy animals also became ill when inoculated subdurally with an emulsion of brain substance from animals inoculated with herpes virus. Blanc and Caminopetros were able further to infect the corneas of other animals with emulsions of the brain substance taken from animals in which the corneas had previously been inoculated with herpes virus. These experiments have meanwhile been confirmed by many other investigators.

Position of the Herpes Simplex-Releasing Agent in the General Group of Disease-Producing Agents.—Even if one must still admit that the agent producing herpes is morphologically unknown, experimental biologic work has at least made it clear that herpes simplex is of a uniform nature, i. e., that it is always produced by one and the same agent and, as one must assume, by a living agent.

Pathogenesis of Herpes Simplex; Its Provocation by Endogenous and Exogenous Factors.—The facts which animal experimentation disclosed in the investigation of the pathogenesis of herpes simplex are of special interest to neurologists because they reveal extensive analogies with certain inflammatory (infectious) diseases of the central nervous system. Evidence for the existence of herpes virus outside of the herpes vesicle at the time of the herpes eruption has been repeatedly presented; the virus has also been found outside of the eruption in patients convalescing from herpes.

The view held by various authors, especially Löwenstein, that herpes virus transitorily circulates in the blood of human beings is still debatable. Up to the present time, the virus has not been found in the cerebral fluid of human beings. The findings of Bastai and Busacca do not withstand critical examination.

To summarize, one might say that biologic proof of the existence of a specific virus has been demonstrated with certain regularity only in the contents of the herpes vesicles; it has been found repeatedly in the saliva, in isolated cases even during the eruption-free interval, but not with certainty in the blood and spinal fluid of human beings. Herpes simplex can be transmitted not only from one area of skin to another in the same patient but from person to person, as was shown by Teisser, Gastinel and Reilly in 1923. They found that the transmission from person to person occurred more expeditiously when increased appearance of herpetic conditions existed than at other times. This fact can be explained only by assuming that the organism must be prepared or predisposed in a definite manner in order to fix the virus at the point of inoculation, unless one wishes to assume that the virus possessed a special virulence at certain times, for which there is no adequate proof. The authors cited could also demonstrate that susceptibility in the individual case is subject to great variation, that the inoculations are particularly effective when the inoculated person is suffering from a definite infectious disease and that inoculation is favored by all diseases that are usually associated with herpes, e. g., pneumonia and epidemic meningitis.

It is interesting that the reaction during the acute phase is different with various infectious diseases. Artificial production of herpes, for example, occurs more readily in rubella and in scarlet fever than in measles. Factors within the inoculated person may hinder or impair the appearance of a herpes eruption (e. g., in hemiplegic patients on the paralyzed side), a fact that is probably to be attributed to a trophic-vegetative disorder. Why herpes simplex arises spontaneously in many infectious diseases is a question that still remains unanswered.

In view of the facts of clinical and experimental experience, this much can be said for the problem of herpes as well as of acute infections generally: The occurrence of a herpes eruption requires a concurrence of many factors within the organism. There is today no doubt concerning the uniformity of the agent that causes the eruption.

The Extension of the Herpes Simplex-Exciting Agent in the Animal Organism and Its Effect on the Nervous System.—The herpes simplex virus, as far as is known, possesses spontaneous pathogenic qualities only for human beings, but not for other animals. As has already been stated, the virus possesses encephalitogenic qualities for rabbits when artificial infection occurs. The ability of the herpes virus to spread through nerve pathways is a feature which differentiates it from the bacterial and protozoid excitants of disease. It shares this quality with certain other types of virus which cause infections of the central nervous system (poliomyelitis, lyssa and Borna's disease of horses).

If one inoculates the contents of a herpes vesicle on the scarified cornea of an experimental animal, a more or less severe keratitis with associated conjunctivitis generally occurs within forty-eight hours. If the virus does not succumb on the cornea, the process affects the nerve centers belonging to the cornea, i. e., the ganglion ciliare and later the gasserian ganglion. Thence it spreads to the region of the pons, and first confines itself to the ascending roots of the trigeminal nerve; it may exhaust itself here, but more frequently it rapidly spreads diffusely to other centers and pathways. About four days after the inoculation, the animal strives to keep its head turned toward the inoculated side. Soon the animal moves around in a circle in the direction of the affected eye. If the cerebral process spreads beyond the pons, further neurologic symptoms appear: paresis, convulsions, etc.

Encephalitis is produced by injection of the contents of a herpes vesicle directly into the brain, and convulsions are usually present. The symptom picture of herpetic encephalitis is in large measure dependent on the site of inoculation.

Much literature has been devoted to the question of the route by which the herpes virus spreads in the animal organism. Observation has shown more and more that spreading of the virus through the circulation is exceptional. The absence of inflammatory changes in the internal organs, even with most severe herpetic encephalitis, leads one to conclude that a special neurogenic mechanism of extension of the virus exists. This assumption is confirmed by the investigations of Goodpasture and Teague, Marinesco and Draganesco, Rose and Walthard, and others. The first signs of inflammation beyond the cornea are seen in the ganglion ciliare and then in the gasserian ganglion.

That the extension of the herpetic process follows along the nerve pathway becomes a certainty when one considers the results of intraneural inoculation. Herpes virus inoculated into the nervus ischiadicus, within a few days produces myelitis of the lumbar segment of the cord, and inoculation into the nervus medianus, myelitis of the cervical segment. The process remains localized only for a short time. It soon becomes diffuse and extends to the brain if the animal does not die in the meantime. With neural inoculation, the route of extension is as follows: (1) peripheral nerve; (2) spinal ganglion, and (3) spinal cord. An extension of the virus to the central nervous system may also follow injections into the musculature and the mucous membranes, and, as Gildemeister has recently shown, may occur after injection into the skin.

Does an Etiologic Relationship Exist Between the Virus of Herpes Simplex and the Virus of Epidemic Encephalitis?—It is known today that encephalitis epidemica—from the etiologic standpoint—is a nosologic unity. Pette believes that in recent years one has attached disease pictures and symptom pictures to encephalitis epidemica which unquestionably do not belong to this condition.

The majority of organisms that have been claimed to be the excitants of epidemic encephalitis fall into two main groups: (1) bacteria, or nonfiltrable organisms, and (2) filtrable, or invisible, organisms. Important considerations can be produced against the view that the excitants of encephalitis epidemica are

bacteria. This refers in particular to Rosenow's work wherein he claims that epidemic encephalitis and related diseases, like poliomyelitis, are due to streptococci or their toxins. The work of Flexner and his school makes it highly probable that the findings of Rosenow and his co-workers resulted from mixed infections. Neither the work of Rosenow or Kling can withstand careful criticism.

The claim that herpetic encephalitis and epidemic encephalitis are identical provoked lively opposition. Pette believes that there is no conclusive evidence to support the assumption that the viruses are identical. Stern has advanced important objections to the theory of Levaditi and Doerr. Of the many objections to this theory, a few important ones are as follows: 1. It is known that after inoculation of herpes virus into an experimental animal an encephalitic process can be produced with great facility even with very small doses. In contrast to this is the fact that of the many inoculations that have been made to discover the virus of epidemic encephalitis, only an extremely small number were successful. 2. Encephalitis epidemica selectively attacks definite centers with great regularity. Herpetic encephalitis, or more correctly, encephalomyelitis, of experimental animals does not display such selectivity. According to present knowledge, one can only conclude that a close biologic relationship, perhaps a group relationship, exists between these two types of virus.

Other Types of Virus That Show Close Biologic Relationships with Herpes Virus (Poliomyelitis, Lyssa, Borna's Disease).—The peculiar ability of herpes virus to spread along nerve pathways—whether by way of the axis cylinders or via the lymph pathways accompanying the nerves—is also shared by the viruses of poliomyelitis, lyssa and Borna's disease. Most authors agree that these types of virus are biologically closely related or belong to the same "group." F. H. Lewy has justly pointed out that the microscopic visibility or invisibility of a disease excitant cannot be considered a criterion for determining its grouping. The invisibility may perhaps be due to the inadequacy of the optical method. Lewy considers the division into "filtrable" and "nonfiltrable" types incorrect. He believes that there is no essential difference, biologically, between these types of virus and the bacterial or protozoid excitants. He bases his conception on the changeability of bacterial and virus diseases, and points out that visible organisms can be reduced into an invisible, filtrable form.

The types of virus associated with the diseases mentioned, including herpes virus, have certain characteristics that are biologically foreign to bacterial and protozoid disease excitants. Pette mentions their marked resistance to low temperatures as well as their resistiveness to many disinfectants. They may be preserved for years in glycerin, as Rhoads of the Rockefeller Institute has demonstrated with poliomyelitis virus. A further important phenomenon is the impossibility of growing cultures on the usual bacterial mediums. Cultivation of these different types of virus is possible only in living organisms. From this one may conclude that their growth or multiplication is confined to the living cell.

BOLTZ, Binghamton, N. Y.

SPINAL SYPHILIS UNDER THE PICTURE OF AMYOTROPHIC LATERAL SCLEROSIS. H. KAISER, Ztschr. f. d. ges. Neurol. u. Psychiat. **136**:798, 1931.

Kaiser collected eighty-one cases from the literature in which syphilitic changes in the pyramidal tracts were combined with similar changes in the anterior horn cells. He divides these cases into two types: 1. The poliomyelitic type, composed of cases in which changes in the pyramidal tract were slight. These can be divided into two subgroups: (*a*) those with increase of reflexes and an isolated Babinski sign (thirty-four cases); (*b*) those in which amyotrophic changes were demonstrated only pathologically (eight cases). Raymond and Cestan stated that 50 per cent of the cases of amyotrophic lateral sclerosis are more or less pure amyotrophic cases. 2. The spastic type. This is rarer and gives the classic picture of amyotrophic lateral sclerosis (thirty-nine cases).

Kaiser reports a case from Foerster's clinic. The patient, aged 58, had been well until 38. At that time he noticed weakness of the left hand and wasting of the muscles, first in the biceps and later involving the entire arm, which became powerless. There were no pains or paresthesias. In 1910, Foerster diagnosed the case as syphilitic muscular atrophy of the Duchenne-Aran type and treated the patient with arsphenamine. The condition was quiescent for thirteen years. Seven years before entrance weakness in the muscles of the neck developed with inability to hold up the head, and one year later the process progressed to the right shoulder and arm. It proceeded to involve the right hand. Spasticity of the lower extremities developed. For a year before entrance there were headache, vertigo and diplopia. Hearing was difficult for nine months before entrance. Examination showed the head slumped forward and the cervical vertebrae fixed in kyphosis. The neck musculature was atrophied. There was atrophy of the upper extremities and spasticity of the legs. The spinal fluid showed 47 leukocytes and 49 lymphocytes, a positive Wassermann reaction and increased globulin.

In classic cases of amyotrophic lateral sclerosis, syphilis is an etiologic factor in 8 per cent. This number is doubled if one includes cases of syphilitic amyotrophy with mild pyramidal tract signs. Léri and Leronge were able to collect eighty-one cases up to 1913 with syphilitic muscular atrophy and pyramidal tract signs.

The first symptom is usually weakness of the small muscles in one or the other hand. Fibrillations and even spasms of the muscles may take place in the affected areas. After a period of quiescence of a few weeks or months, the process involves the extensors of the forearm or it may jump to the biceps. The process then progresses slowly to the other arm. Spastic symptoms then set in in the lower extremities. Bulbar symptoms may set in in the late stages, as well as difficulties in defecation or urination. In twenty-three of thirty-six cases (64 per cent) the disease began in the small muscles of the hand. Only four times (11 per cent) did it begin in the muscles of the shoulder. Most often the patient noticed an inability to lift the arm, and this led to the discovery of atrophy of the shoulder muscles. In four cases (11 per cent) the legs were first affected by a peroneal palsy, the so-called peroneal type of syphilitic amyotrophic lateral sclerosis. When the disease begins with bulbar symptoms, it progresses rapidly, with inability to swallow and death. The average duration of syphilitic amyotrophic lateral sclerosis is six years. This average was taken in cases with a rapid course. There are many cases that run a slow course of about twenty years.

Men are usually affected (thirty of thirty-six cases). The age varies between 22 and 59, with an average age of 42. The disease occurred, on an average, eleven and one-half years after the infection, the range being from ten months to twenty-nine years. The first symptom noted in almost all cases was motor weakness. Martin put the muscular atrophy in these cases at 77 per cent. The muscular atrophy and weakness are asymmetrical in occurrence; first there is affliction of one hand, arm or shoulder, followed by similar changes in other parts. Fibrillary twitchings or myoclonus occurs in 50 per cent of the atrophied muscles. Evidence of pyramidal tract involvement is found in the hyperactive patellar reflexes, spasticity, Babinski sign, etc. Lateral column signs are found as a late symptom; they occurred as an early symptom in only four cases. In 27 per cent of cases there were bulbar symptoms. In five cases bulbar symptoms ushered in the illness and were followed rapidly by death. The symptoms usually consisted of bulbar speech, fibrillary twitchings of the tongue, disturbances in swallowing, breathing and the like. The Argyll Robertson pupil occurs as a cardinal and extremely important symptom. It was not found in all cases. There were pupillary changes in 52 per cent of the cases. Spiller alone has observed complete stiffness of the pupil to light, with retention of accommodation reaction. Sluggish light and accommodation reactions were seen in seven cases; anisocoria, in eight cases. Extra-ocular palsies occur, but are rare. In 41 per cent of the cases there was retention and incontinence of urine. In 23 per cent the disease was ushered in by pains or paresthesias for a shorter or longer time before the

occurrence of motor symptoms. In four cases there were sensory disturbances, thermanesthesia and analgesia (Olivier and Halpré), slight ataxia (Spiller) and slight vibratory disturbances (Martin). Sensory disturbances are rare, however, and should always throw doubt on the diagnosis of amyotrophic lateral sclerosis.

In 79 per cent of cases there was a positive Wassermann reaction of the blood, and in 69.5 per cent the Wassermann reaction of the spinal fluid was positive. Globulin was always increased; the cells averaged 28; albumin was increased in 100 per cent of cases.

There are thirteen cases of syphilitic amyotrophic lateral sclerosis with necropsy. These fall into two types: 1. Cases with marked inflammatory changes in the meninges and vascular apparatus. 2. Cases in which the parenchymatous changes in the cord are most pronounced and in which inflammatory changes in the meninges and vessels are of minor importance. Only two cases of this type have been reported.

The chief changes in the spinal cord are: 1. Chronic meningitis, running the entire length of the cord, even reaching the cortex, and characterized by thickening of the vessels, and lymphocytic and plasma cell infiltration. 2. Chronic myelitis, most marked at the periphery and most marked in the cervical cord. Here there is thickening of vessels, perivascular infiltration with lymphocytes and plasma cells, proliferation of glia and glia fibrils, ependymitis, atrophy of the anterior horns, with degeneration of the anterior horn cells, and unsystematic degeneration of the lateral columns. This is the typical picture of a meningomyelitis. None of these changes is specific. It is only when the spirochete is found that the specificity of the process is certain. This has never been found as yet. The peripheral nerves show no atrophy.

In the second type described, the pathologic changes are characterized by: 1. Changes in the parenchyma of the cord with atrophy of the anterior horns and degeneration of the ganglion cells, degeneration of the crossed and uncrossed pyramidal tracts, proliferation of glia and some perivascular infiltration. 2. A mild chronic meningitis.

ALPERS, Philadelphia.

PROJECTION IN NORMAL AND IN MENTALLY ILL PERSONS. G. JELGERSMA, J. f. Psychol. u. Neurol. **43**:209, 1931.

Jelgersma discusses projection in normal persons and in those suffering from endogenous and from toxic psychoses. Its mechanism is identical in all cases in which it occurs. It always occurs whenever a person is unable to trace further into the past the cause of any psychic process. He then says to himself, "I have no influence over this process; it is not mine; it is not my property; it arose in my environment; it belongs to my external world." It is for this reason that people must assume an external world and separate sharply the world of perception from the ideational and volitional worlds. The borderline of these is occupied by the memory world, which may be influenced by perceptions as well as by ideas; it originates externally and is recalled from within. When a psychic process, recognized normally as coming from within, cannot be recognized as such and, owing to this, is attributed to the world of perception and is regarded as a perception, hallucination or delusion, the projection is pathologic in nature. In the case of a properly projected hallucination and delusion there can be no question of contradiction or correction, because the patient cannot contradict himself as far as his own inner world is concerned.

In pathologic conditions it may be said that, as a general rule, proper projection occurs in the toxic but not in the endogenous psychoses. What actually does occur in the latter is illustrated best in cases of depression, with accusatory delusions in which projection does not occur at all, and which cannot be regarded as true delusions but rather as symbols that are localized in the patient's own psyche. In mania, too, there occurs no projection, although one can find traces of what is designated in present terminology as formation of delusions. The very feeling of exaltation leads to an overvaluation of the patient's personality not unlike

that observed even in normal man. Another form of pseudodelusions of grandeur is observed in persons subject to bragging and boasting. The inconstancy and variability of these pseudodelusions give the impression that the person does not believe them himself and that they represent an expression of his happy or irritable mood. It is only when there is a schizophrenic interpolation into the manic symptom complex that projection and with it a formation of delusions and hallucination take place. The only reason why there is a greater tendency to delusions in melancholia is that the melancholic affect, viewed objectively, is undoubtedly more intense than the manic affect.

In hysteria, too, there is no proper projection of the hallucinations, popularly called visions; they are momentary phenomena, appearing only in the acute attack; they resemble mistakes which are believed by the patient for the moment but are soon corrected; they are memories that, under the influence of an affect, may be unreal but are soon properly evaluated; they appear only in the visual sphere. There are no delusions in hysteria. There is only one endogenous psychosis which, according to Jelgersma, resembles hysteria and in which objectivated delusional ideas occur without hallucinations, and that is paranoia. This disease belongs to the endogenous psychoses because it develops under the influence of normal external life. One must, however, bear in mind that the basis of the disease is a character anomaly usually associated with more or less pathologic projection, because the patient believes that the external world is more or less changed. The stimuli arriving from the external world have no other significance than that they intensify the already existing anomaly. It is also noteworthy that hallucinations almost never occur in paranoia. In this respect it differs from hysteria, in which no delusions are observed but in which hallucinations are unusually common, although, as has been said before, they have an entirely different significance in that their projection is superficial, flighty and easily corrected. This may also be said to be true, though to a lesser extent, of the delusions in paranoia. These are objectivated and projected in the same sense as in schizophrenia, but in the course of time they become less marked and, as has so frequently been observed among querulant persons and erotomaniacs, they may disappear entirely and become merged with the patient's previous character anomaly.

There are two other functional psychic disturbances that resemble projection but are observed only in pathologic conditions; they have no analog in normal psychic life. They are introjection and extrojection. Introjection occurs in melancholia and may also be elicited analytically in other mental diseases. In introjection, the external psychic components of the personality are thrown into the inner psychic life and accepted by the unconscious. The external perception is normal, but its acceptance by the inner psychic life and its elaboration by the latter is pathologic. In this sense introjection may be regarded as an attempt at correction of an external impression or as a reattachment to the love object. According to Freud, the self-accusations of a person suffering from delusions of sin are not directed toward himself but toward the object. Of course, the entire process of introjection remains unrecognized by the patient. Introjection plays an important rôle in melancholia, especially with delusions of sin, as well as in hysteria. In introjection, then, something is derived from the external world which has been accepted by the patient and has become a part of his inner psychic life. In contradistinction to this, in extrojection there is something within the patient that is unpleasant and disagreeable to him, and, as he does not desire it, he casts it off to some other person. In many cases it is an attempt to throw off something of which the patient is ashamed. In a certain sense it is more than a projection. It indicates that the patient is passing on to another person something that he does not want. In projection there also occurs a passing on of something disagreeable, but it is to the external world at large and not to another person. Furthermore, pathologic projection is not merely a process of passing something on to the outside world; it also represents a certain symbolization, whereas extrojection is a process of passing something on to the outer world at the same time that the inner psychic process remains unaltered.

KESCHNER, New York.

WAYS IN WHICH DISTANCE OF THE TEST FIELD AFFECTS DETERMINATIONS OF RETINAL SENSITIVITY. C. E. FERREE and G. RAND, Arch. Ophth. **7**:383 (March) 1932.

Determinations of achromatic and chromatic sensitivity are affected by such factors as breadth of pupil, size of test field, state of adaptation of the eye, brightness of the preexposure and surrounding field and distance of the test field. That the distance of the test object affects acuity has been at least fairly well known to ophthalmologists and workers in physiologic optics for many years, but that it has an important or considerable influence on retinal sensitivity has received little attention other than what is implied in the control and specification of distance as one of the conditions of work.

According to the laws of geometric projection, when the size of the object is kept constant and its distance is varied, the size of the image should vary inversely with the square of the distance of the object; when, however, the size of the object is changed by the amount required to keep the visual angle constant, the size of the image should remain the same. In both of these cases the change in the refraction situation is a modifying factor. With increase of accommodation the distance of this plane from the retina should become greater, and the size of the image increase; and with decrease of accommodation the distance should decrease, and the image become smaller. This is important in that the size of the image is supposed to have an effect on the intensity of sensation.

Change in the distance of the object causes a change in the size of the pupil and a proportional change in the amount of light condensed into the image. The effect on the sensory response would occur through a change in the intensity of the stimulation. There should be no change in the light density of the image with a constant size of pupil, because both the intensity of light incident in the pupil and the size of the image vary inversely as the square of the distance of the object.

Change in the distance to which the image is projected is a possible psychologic factor and implies some relation between the intensity of sensation and the spatial magnitude of the projected image.

In 1914, Ferree and Rand conducted two types of experiment to determine the effect of distance on the apparent brightness of objects. These experiments were made because certain photometrists, engaged in the development of methods of measuring brightness, were advancing opinions that were difficult to reconcile. Ferree and Rand discovered in two sets of experiments a strong but irregular effect of distance as a factor. They had also carried out experimental work to determine the effect of distance on the value of the chromatic threshold. In this, also, the effect of distance was to decrease the apparent intensity of the response, and in these experiments the conditions were planned to give full effect to all of the following factors: change in accommodation as influencing both the size of the image and the density of light in the image, change in the size of the pupil as influencing the density of light in the image and the sharpness of imagery, and the distance to which the image was projected as a psychologic factor.

In presenting the ways in which the decrease of the test field affects determination of retinal sensitivity, the authors refer in detail to a paper they published in 1911, relative to the spatial values of the visual field immediately surrounding the blind spot and the question of the associative filling-in of the blind spot. In this paper experiments were reported in which subjective magnification of space value was produced in order to see whether in those cases in which the amount of magnification could be subjected to variation and control there was an effect of magnification on the intensity of the sensory response. One of the obvious ways of producing this magnification is the projection of the image to different distances. A detailed summary of the conditions obtained in the experiments was given, because the distance of the object and the accommodation always being the same, the size of the image was always the same. The size of the pupil was controlled so that it was always the same by variation in the saturation of the color to give the different values needed for the threshold without change in

brightness. The projection fields were all carefully matched in brightness. The determinations were made under controlled illumination and mechanical arrangements, whereby projection of the after-image was allowed without moving the eye. Different observers were used, and the series was repeated on each observer on different days. They concluded that there was a well marked effect of the distance of projection in the value of the after-image threshold, and that the amount of light required to arouse the after-image was found to increase as the distance of projection of the image was increased.

There seems, then, in general, to be an effect of distance as a factor in the determination of retinal responses, even when narrowed down to the distance of the projection of the image. Whether or not there is a differential effect for the different colors remains to be determined.

Further, distance should be given consideration as a factor in determination of sensitivity at the center of the field and in work on the perimeter and tangent screen. As a matter of practical procedure, therefore, it is in the determinations of central and peripheral sensitivity to light and color and in the use of the tangent screen for comparative purposes at different distances that the effect of the factor has in particular to be looked out for and guarded against.

SPAETH, Philadelphia.

PRINCIPLES OF PSYCHOTHERAPY IN PSYCHOSES. PAUL SCHILDER, Psychiatric Quart. **5**:423 (July) 1931.

The author first reports the case of a woman, aged 25, who had been treated for paranoid schizophrenia by him by hypnosis. A transference was effected and was followed at once by a relief of the symptoms. The transference was not dispelled at the time when the patient was discharged and she was unable to make an erotic adjustment. Two years later, there was a recurrence of the paranoid ideas, and the patient was treated by a second physician. This man was unable to get in contact with her, and a transference was not effected, the method of treatment being psychotherapy. The author saw her for the second time and found her with many delusions, mostly of a sadistic type. At this time he was unable to get into contact with her. Because the analyst does not know what goes on in the mind of a patient with a hypnotic transference it is a difficult transference to manage. In this instance the patient was discharged by the analyst when he knew that there was no lessening of the transference, for the reason that he feared that the symptoms would recur. He realized that there was not a full recovery but expressed surprise that the patient had not found a love object, that a relapse had occurred, and that in the second attack she was so resistive to psychotherapy.

Schilder believes that the first and second attacks differed in that the second was more severe because the libido was immovably fixated in the symptoms. As a disease progresses there is less libido at the disposal of psychotherapy, regardless of the kind used, because of the great amounts invested in the early points of fixation. This he believes is one of the barriers in the psychotherapy of schizophrenia.

Hysteria, anxiety, obsession neuroses and compulsion neuroses have been called transference neuroses because of the fact that transference is easily obtained. Such transferences start from the fully developed Oedipus complex as well as the lower pregenital type. A successful analysis is based on the genital type: the Oedipus complex and the lower types, anal, oral and sadistic, may be revealed but it is not possible to base an analysis on them. In the neuroses a transference may be accomplished by the free association method, but in schizophrenia the transference must be won in a more active way. Therefore the object cathexis is enforced at the beginning of treatment.

The second phase of every psychotherapy in a neurosis as well as a psychosis is the use of the transference. In hypnosis the transference is used to elicit forgotten material or to educate the patient. In the psychoanalysis of a neurosis the

transference is used to uncover infantile situations that have influenced the life of the patient; at the same time the ego-ideal is dissolved and rebuilt. Neurotic and normal patients can rebuild by their own force an ego-ideal and need no help. In the schizophrenic patient this is not true; if he is told he has homicidal impulses he may agree, and because of the weakness of the ego plus super-ego system he may act accordingly. An important difference in the technic of the analysis of the neurotic and the psychotic patient is that in the latter it is a question how far the patient is able to stand the coming out of primitive material, and in the neurotic the question is: Can the ego system of the patient stand the primitive material? With the neurotic person there is seldom the opportunity to order the patient to be more moral and not to let himself go too much; with the psychotic this principle of education is needed. In the neuroses there is a strong trend of logical thinking which must be broken by the free association method; in the schizophrenic psychosis a sharp differentiation between the systems of consciousness and unconsciousness does not exist. Conversation will often substitute for the free association method.

The third phase of psychotherapy in a neurosis is the breaking of the transference; treatment is not complete until this is accomplished. In schizophrenia it is not as important, and sometimes it is necessary for the patient to retain dependence on the physician.

In manic-depressive psychoses, besides an oral regression there is a change in the relation between the super-ego and the ego. In melancholia the super-ego is severe toward the ego and the gap between the two is increased. In mania, ego and super-ego are united. In melancholia, the patient is so much concerned with torturing himself that it is difficult to get the necessary amount of libido. The severity of the super-ego has to be appeased or the person consoled; otherwise the danger of suicide will be increased. This danger may be increased during psychoanalytic treatment. In mania a transference is easy to get but difficult to retain because of the tendency to drop the love object. Psychoanalysis is generally impossible and unnecessary.

The author believes that psychotherapy can be aided by somatic treatment. If a patient is put to sleep, the structure of the libido is changed and more primitive sexuality comes out. Hypnosis and transference are increased by drugs. Sleeping medicines bring the psychosexuality nearer to the more infantile sexuality of dreams. Mecaline and cannabis indica bring stages that resemble narcissistic schizophrenic regression. Cocaine intoxication brings a paranoid picture to the foreground, and its chronic use produces homosexuality from heterosexuality. Cures of schizophrenia and manic-depressive psychosis have been reported with the use of deep sleep. The patient regresses to a more infantile stage, becomes helpless and seeks help in such a prolonged sleep. It is possible that by the use of drugs resistance can be lessened and a transference increased.

HOWARD, Milwaukee.

THE BRAIN IN PAGET'S DISEASE OF THE SKULL. E. GRÜNTHAL, Ztschr. f. d. ges. Neurol. u. Psychiat. **136**:656, 1931.

Marie and Léri called attention to the changes in the skull in Paget's disease, naming the deformity which results *convexobasic*. They described a narrowing of the posterior fossa, the relative raising of the circumference of this opening, the pushing forward and horizontal position of the occipital bone and finally the relative sinking of the anterior fossa. The skull shows, as a result of this deformity, a definite convexity upward. The changes in the skull produce a more or less pronounced pressure on the under side of the brain, on the medulla in the posterior fossa, on the nerves and vessels which run through the foramina at the base and on the cerebellum. Clinical signs of involvement of the brain and the cerebral nerves are not rare and often lead to an early diagnosis. Schaen called attention to the larval form of Paget's disease in which the bone changes are not yet apparent clinically but in which the inner thickening of the skull causes

symptoms of a neurologic nature. Recently, Nonne has reported on the neurologic symptoms of Paget's disease: headache, epileptiform attacks, visual disturbances, auditory disturbances, olfactory symptoms, sensory disorders, neuralgias, spinal cord paralyses, vomiting and loss of teeth. Cerebellar disturbances, which are often mentioned in the literature, were not listed by Nonne.

Grünthal reported the anatomic findings in a case of Paget's disease with cerebellar signs. While these are commonly seen clinically, they have been studied but rarely pathologically. Koch reported a brain in which the cerebellar hemispheres were thinned to about 2.5 cm. Both frontal lobes were much decreased in size, especially at the base; the temporal lobes were hollowed out mesially through thickening of the sphenoid, and the pons was flattened out. The optic chiasm was flattened, but the optic nerves were unchanged grossly.

The only other case with anatomic study is that of a patient of Grünthal. The first symptoms appeared at 30 years of age. Two years later, there were bony excrescences and softening of the head. Five years later, the circumference of the head was much increased. At this time, nothing was found neurologically. Subjectively, there were headache and apathy. One year later the patient noticed that he had lost height; in a few years he looked a typical dwarf. Epileptiform attacks developed four years later, and nine years after this a period of unconsciousness lasting several days occurred. About twenty-three years after the onset of the trouble, headache, visual and auditory disturbance, epileptiform attacks and a static auditory disturbance developed. At this time the skull was enormously thickened. Roentgenograms showed the typical picture of Paget's disease. The patient died at 57 years of age, twenty-seven years after the onset of the illness. At necropsy, the skull showed the typical picture of *convexobasie*. The brain showed a compression of both cerebellar hemispheres, the left more than the right. The left parietal lobe appeared flattened. The hypothalamus, pons and periaqueductal gray were flattened, particularly the pons. Section of the cerebellum confirmed the flattening, and it was found that the cerebellar hemispheres were about half their normal size. The compression of the basilar structures was due to the marked thickening in the sphenoidal bone; that of the cerebellum was due to the bony changes in the posterior fossa. The lateral and third ventricles were dilated. Microscopic study of the cerebrum showed nothing except an accumulation of fat in the nerve cells and neuroglia everywhere in the cerebrum and cerebellum. Myelin sheath studies of the compressed basilar structures, pons, etc., showed no changes. The most marked changes were in the cerebellum. Here, especially in the anterior part of the right lateral lobe, the Purkinje cells had disappeared entirely, and the layer of Bergmann cells was proliferated. In the molecular layer there was a definite proliferation of glia fibers. The tangential fibers, mossy, climbing and basket fibers were little affected. The granules showed few changes. In the folia that were not completely compressed there was disappearance of the Purkinje cells, depending on the degree of compression. Other cellular elements were not affected. The dentate nucleus showed a loss and shrinkage of cells in the basal portion, and also a loss of fibers in this area. This portion is in direct connection with the Purkinje cells, and the centrifugal fibers had undergone secondary degeneration.

Therefore, despite prolonged compression, the brain showed few changes and the changes that were found were confined to the Purkinje neurons. One is therefore dealing with an elective centrifugal cerebellar atrophy in the sense of Bielschowsky. Such cases occur late in life and are caused by alcohol, nicotine, bladder infections, arteriosclerosis, senility and hereditary factors. None of these cases explains the disappearance of the Purkinje cells.

Grünthal's case indicates that a cause of the systematic cerebellar atrophy may be pressure against the cerebellum as seen in his case, since the loss of Purkinje cells was found only in places where there was compression. In other words, a system within the brain was destroyed by pressure from without. The mechanism was a "system type of injury" (Spielmeyer), or *Pathoklisis* (Vogt).

ALPERS, Philadelphia.

ON THE INTERRELATIONSHIPS BETWEEN PSYCHIC AND VEGETATIVE FUNCTIONS. W. R. HESS, J. Nerv. & Ment. Dis. **74**:301 (Sept.); 511 (Oct.); 645 (Nov.); 726 (Dec.) 1931.

The work of Specht and Kuppers and advances made in the investigation of the vegetative nervous system have stimulated the author to study the relationship to the psychic processes on the principle of reciprocal and coordinated functions. The relation of the vegetative to the sensorimotor nervous system is discussed, and evidence of this reciprocal action is adduced. The author conceives that the sensorimotor principle comes into being at the appearance of the metazoa or when the cells combine to form a commonwealth of cells. In the lower animals little light has been thrown on the relationship of these two systems, but it has been supposed that they stand in closer cooperation than in more highly differentiated organisms. The preservation of the life of the cell, regarded as the aim of the vegetative nervous system, is in harmony with the preservation of the total organism, which is the function of the sensorimotor system; however, in the control and direction of the circulation of the blood the two systems exhibit antagonism. In strenuous exertion of the total organism the sensorimotor system dominates the vegetative, while in the condition of fatigue the reverse is true. This reciprocal antagonism and interdependence is illustrated in the regulation of the heart action, which, however, never yields exclusively to either inhibiting or stimulating influences, but tends to reach a condition of equilibrium between the two antagonists. Within the vegetative nervous system there is the same reciprocal antagonism between the two divisions, the sympathetic and parasympathetic, the former performing a rôle analogous to that of the sensorimotor system in regard to the total organism and even appearing as a connecting link between the sensorimotor and vegetative functions. On the other hand, the parasympathetic nervous system produces a diminished efficiency in the sensorimotor apparatus.

The phenomenon of sleep is now regarded as a positive adjustment within the organism rather than as a functional insufficiency, and the observations of Claparède, Verworn, Kreidl and Herz, Tromner, Maunther and Kuppers are discussed in this regard. The author considers sleep a mechanism by means of which the vegetative regulatory system exercises its influence on the sensorimotor nervous system, producing a diminished functional preparedness through a shifting of the equilibrium to the parasympathetic from the sympathetic influence. That the extinction of consciousness in sleep is associated with the suppression of sensory stimuli is well known. Disturbed psychic function can be the expression of a disturbance of the equilibrium between the two divisions of the vegetative system. Some space is devoted to the study of pupillary constriction in sleep. This constriction is followed by a marked dilatation when the subject is aroused; it is to be interpreted as a means of reducing the stimuli to the retina and of restoring the functional ability of the organism by vegetative regulation. Similarly, the diminished excitability of the tendon reflexes during sleep is regarded as a reduction of the functional preparedness in the sensorimotor system.

Alterations of ocular sensitivity by means of pilocarpine were studied. This drug is parasympathetic in action but is more readily diffusible than ergotamine. Injections into the lateral and third ventricles of the cat were made under good chloroform narcosis. After the cat recovered from the narcosis, a diminution in psychic activity similar to sleep was observed and was attributed to injection of ergotamine. In this state the pupils contracted more and more, as in sleep, but when the cat was aroused, the pupils dilated again promptly, as in the normal waking response.

Cocaine has pronounced sympathicotropic qualities, with acceleration of psychic functions and of the sensorimotor apparatus. Thus, hyperacusis and increased ocular sensitivity are noted. The drug's action seems to give fresh evidence of the regulating influence that the vegetative nervous system has over psychic activity.

The author concludes that there is a harmonious mutual participation of sensorimotor and vegetative nervous system, in which there is an alteration in the

domination of one system over the other during the catabolic and anabolic phases of the organism's activity. A disturbance in this equilibrium leads to disturbance in psychic functions.

HART, Greenwich, Conn.

MODIFICATION OF THE HISTOLOGIC PICTURE OF THE CORPUS STRIATUM IN PERSONS DYING OF VARIOUS DISEASES. C. BERLUCCHI, Riv. di pat. nerv. **38**:152 (July-Aug.) 1931.

In order to establish the histopathologic value of lesions that are supposed to be characteristic for extrapyramidal diseases and are located in the corpus striatum, the author has examined, in the cases of fifty-five persons dying of various general diseases, including some neurologic conditions, the various histologic elements such as the nerve cells, nerve fibers, glial elements and blood vessels. The ages of the patients varied from birth to senility. Hence the author took cognizance of the variations due to age. The inspiration for the work was given by the fact that the number of cases is increasing in which lesions of the corpus striatum are not accompanied by the clinical manifestations considered by the Vogts as characteristic of the extrapyramidal conditions.

The conclusions reached by the author are that lesions may be found in the corpus striatum in general medical conditions in which no symptoms seem to point to an involvement of these structures. The most important facts gathered by the author may be summarized as follows: 1. Nerve cells of the striatum, both small and large, normally vary extremely from person to person even in the absence of true neurologic conditions. Fundamental general factors, such as the circulatory and the toxic ones, the length of the agonal period and, possibly, a variation of resistance in various persons may be sufficient to produce histochemical modifications of the cytoplasm or of the nucleus of the nerve cells. Such modifications are so frequent that at times it is even difficult to establish what might be considered a normal picture. 2. The small nerve cells of the striatum disclose, more frequently in subjects not suffering from a disease of the nervous system, the presence of numerous satellites; at times these cells also undergo a process of gradual fading and subsequent diminution in number. Such a disappearance of small cells, which had been described only in extrapyramidal diseases, is considered by the author to be of considerable importance as pointing out the great vulnerability of those elements to the most varied pathogenic conditions. 3. An important fact disclosed by Berlucchi is that even in a person as young as from 15 to 20 years substances stainable by the Herxheimer method are found in the small cells of the striatum, and that in subjects as young as from 25 to 30 years pigment is to be found in the same cells. 4. The nerve cells of the globus pallidus in various general conditions may disclose a severe lesion of the chromatic substance of the nucleus and of the processes. In some instances the diseased elements predominate over normal ones. 5. The nerve cells of the globus pallidus contain in adults and in old persons a pigment which at times fills the entire cell body. This condition, which has been considered by some authors as characteristic of paralysis agitans, may therefore be normally found in simple senility uncomplicated by an extrapyramidal condition. 6. With an appropriate stain for myelin, at times the distribution of myelin is such as to resemble status marmoratus and at others, a condition of apparent fibrosis. 7. The myelin sheaths of the globus pallidus frequently undergo a process of rarefaction, at times patchy, at others diffuse, eventually simulating the so-called status dysmyelinisatus, which is often accompanied by concretions of fat, pigments and pseudocalcium in the globus pallidus. 8. The astrocytes of the striatum, especially in aged persons and in adults, less frequently in young people, undergo a process of hypertrophy accompanied by moderate hyperplasia. Such changes are apparently the same as those often described in Huntington's chorea. The astrocytes of the globus pallidus also undergo progressive changes and frequently disclose the presence of nuclei of the type described by Hallerworden and Spatz in the disease that bears their name. 9. The blood vessels of the striatum, in a large number of old persons, undergo

severe arteriosclerotic changes that often are accompanied by disintegration of the surrounding perivascular tissue without concomitant clinical symptoms pertaining to the extrapyramidal conditions.

Altogether, though the author is somewhat careful in expressing a definite conclusion, it seems that the main object of his work is to call the attention of histopathologists to the importance of lesions of the corpus striatum in general medical conditions not of the extrapyramidal type, and to emphasize that these lesions may not vary in extent and intensity from those described in the so-called extrapyramidal diseases.

FERRARO, New York.

ABSTINENCE PHENOMENA IN CHRONIC ALCOHOLIC PATIENTS. S. G. JISLIN, Ztschr. f. d. ges. Neurol. u. Psychiat. **136**:645, 1931.

Sooner or later, in every alcoholic patient there appear abstinence phenomena for the amelioration of which alcohol is again desired by the patient. These symptoms appear after a period of abstinence and come on unknown to the alcoholic person. They have been called "episodic phenomena" by Schroeder, but Jislin is convinced that they are not accidental symptoms but pure abstinence symptoms in the narrow sense of the word. Furthermore, they differ from delirium tremens. The first symptom of abstinence is a change of mood that comes on immediately after a period of unregulated drinking. There is an increased fear or apprehensiveness, an uncertainty and a tendency to lack of truthfulness, chiefly in the form of unsystematized, rapidly transitory delusions. At first these are related to the patient's situation; people talk about him or look at him because his face shows evidence of drinking. Gradually, paranoid ideas develop more and more sharply. Somewhat later disturbances in sleep develop; sleep becomes difficult and restless, and often the alcoholic person falls into a state resembling a doze rather than sleep—into unconsciousness, as he terms it. Dreams are unpleasant and often frightful. Later, the dreams become more vivid; the patient falls through something; objects fall on him; he lives through all sorts of terrible adventures. The characteristic of the dream is that everything is unusually active. Tremor is an important symptom of the periods of abstinence. In the first years the phenomena of *Nachrausches* are mildly expressed: in slight tremor, fearfulness and insomnia. All these symptoms become worse with time. They continue for a series of days.

A running description of the symptoms follows: The patient develops tremor, which becomes lasting, and in order to prevent the loss of his job takes a drink. His mood is a bit depressed. He believes that neighbors and friends talk about him, laugh at him or accuse him. Street cars try to run over him. Mass meetings are called on his account. People speak evil of him. His face shows that he is alcoholic. He remains at home in order to evade these annoying experiences. Unusual noises produce anxiety symptoms, such as sweating and palpitation. He hears people calling him. At night he is extremely restless. He will not go to the toilet alone and will not remain alone in a room. Sleep is at first impossible and later restless. He dreams constantly about bandits and fellows with awful faces, about wolves, bears, lions, dogs, cats, mice and horses. The wolves and bears bite him, and he tries to beat them with his hands. He hears bells, cries and music, and wakes in terror seeing the faces of men or animals for a few moments. He fears these periods of "unconsciousness" and so refuses to close his eyes. He often finds trouble in orienting himself and in distinguishing between truth and dream.

The most frequent abstinence symptom is the auditory hallucination. It occurs chiefly, if not exclusively, in schizoid alcoholic persons. Abstinence symptoms are greater when drinking is abandoned suddenly and are much weaker and milder if the drinking is abandoned slowly by decreasing the amount taken daily. The similarity of these abstinence symptoms to delirium tremens is striking, but they differ decidedly.

ALPERS, Philadelphia.

AN ATTEMPT TO CLASSIFY SOME OCULAR SYNKINESES. H. COPPEZ, Rev. d'oto-neuro-opht. **10**:12 (Jan.) 1932.

Coppez discusses physiologic and pathologic ocular synkinesis, the former represented by a synkinetic contraction of the levator of the brow that accompanies voluntary contraction of the superior rectus, and contraction of the superior rectus with voluntary contraction of the orbicularis (Bell's sign). Pathologic ocular synkineses embrace: (*a*) atypical physiologic synkinesis, represented by Graefe's sign, which is an abolished physiologic synkinesis, and the inverted Bell's sign, and (*b*) true pathologic synkinesis, involving the third, sixth, fifth and seventh nerves.

The two principal types of synkinesis of the third pair are: Fuch's syndrome (pseudosign of Graefe), in which, on looking downward, the upper lid is raised, and Stilling's syndrome (active enophthalmos of Morax), which is essentially a monocular congenital paralysis of lateral movements. When adduction is attempted, the globe is buried in the orbit and turned upward. In the syndrome of Marcus Gunn (third and fifth pairs) the lid is raised when the inferior jaw is lowered or when it is carried toward the opposite side. This syndrome is usually seen in patients with congenital ptosis. The syndrome of Friedenwald (sixth pair) occurs in certain cases of meningitis, cerebral syphilis or tuberculosis. When abduction is attempted, the superior lid is raised. It usually appears in patients with paralysis of the external rectus. There are numerous varieties of this syndrome. Hitzig's syndrome (seventh pair) is analogous to Fuch's syndrome. It occurs in the recovery stage of certain cases of facial paralysis. There are several varieties: the palpebrobuccal, in which the eye closes on laughing, or when the teeth are shown; the palpebrobuccofrontal, in which to the preceding is added contraction of the occipitofrontalis muscle; the palpebroplatysmal, in which blepharospasm accompanies contraction of the platysma muscle, and the palpebroauricular, in which the auricle is carried forward when the lids are closed.

Several of the synkineses may be combined. The method of production is: reflex, as in Bell's sign; muscular, illustrated by Stilling's syndrome, in which the muscles of lateral movement are replaced by fibrous cords or in which there is a supplementary insertion of the internal rectus near the posterior pole; truncal, as in the syndromes of Fuchs and of Hitzig, in which there is a derailing of the motor impulse brought about by a transposition of the mutilated fibers during regeneration; nuclear, represented by the syndromes of Friedenwald and of Marcus Gunn. When the syndromes of Fuchs and Marcus Gunn coexist, probably the origin is truncal. Lutz thought that the syndrome of Marcus Gunn was of supranuclear origin, but his hypothesis has not been supported by any anatomic data.

DENNIS, Colorado Springs, Colo.

THE DEMENTIA-PRECOX-SCHIZOPHRENIA PROBLEM. JAMES V. MAY, Am. J. Psychiat. **11**: 401 (Nov.) 1931.

In spite of its great importance, dementia praecox has not been adequately defined or delimited. The disease accounts for more than half of the patients housed in the mental hospitals of the country, and its victims require $40,000,000 a year for their maintenance. The psychiatric literature is deluged every month with statistical reports and psychologic reflections on this subject; yet the subject has not been properly defined. The history of knowledge of dementia praecox is reviewed by a series of direct quotations from the students of this psychosis; each quotation is presented at some length and discussed critically by May. There are, in general, two lines of thought on the subject. Kraepelin was inclined to place the emphasis on the ultimate and apparently inevitable deterioration, while Bleuler considered that the autistic and ataxic thinking (now designated as schizoid) was the fundamental characteristic of dementia praecox. Present psychiatric practice leans largely toward Bleuler's point of view, with the result that the diagnosis of schizophrenia is often reached after the

observation of temporary samples of dissociated thinking and without regard to the life history of the patient. May warns against this hasty and careless practice. Dementia praecox-like episodes may occur in the course of feeble-mindedness, alcoholism, senility or epilepsy, and should not be taken as evidence of schizophrenia. It is the assignment of these syndromes to the dementia praecox group that, May believes, explains the high rate of recovery reported by some observers.

May would define dementia praecox as a dissociation of the personality characterized by incoordination of the mental mechanisms and associated sooner or later with intellectual deterioration. The inadequacy of adjustment, which is an early manifestation of the illness, may be displayed in any of several fields: educational, social, sexual, emotional or economic. Schizophrenia has three characteristic features: (1) primary progressive deterioration, (2) autistic or dereistic thinking and (3) intellectual incoordination. According to the emphasis on one or the other of these features the disease type is brought out. The hebephrenic or simple dementia praecox displays the deterioration, while the catatonic form is characterized especially by dereistic thinking. Schizophrenic persons whose predominant disability is in the field of intrapsychic ataxia and intellectual incoordination are exemplified by the paranoic and paraphrenic groups.

DAVIDSON, Newark, N. J.

HYPERKINESIS. I. I. RUSSETZKY, Encéphale **26**:739 (Dec.) 1931.

The studies reported in this article were based on such clinical conditions as epidemic encephalitic parkinsonism, acute chorea and the dystonia of Ziehen-Oppenheim. The results are given through kymographic records. The effects of synkinesis are shown, i. e., the effects on any given hyperkinesis when some other specific movement is attempted. The author classifies the hyperkineses as follows: (1) Hyperkinesis of trembling. This consists of movements with a rhythm of from 100 to 240 oscillations per minute, with exaggeration under the influence of emotion, cold and cutaneous excitations. These are influenced also by the attitude of the body, but movements produced in other body segments have only a slight effect. Respiratory arrest is without effect, but during sleep this hyperkinesis disappears. (2) Myoclonic hyperkinesis, nonsystemic, with a principal rhythm of from 100 to 120 per minute. Bodily attitudes exert an influence; segmental attitudes and synkineses augment it. Arrest of respiration is without effect, but sleep diminishes or causes it to disappear. (3) Rhythmic systematized bradyhyperkinesis. This consists of oscillations of from 20 to 60 per minute, sometimes stereotyped, sometimes complex. Bodily attitude exerts a greater influence here than in other types, but segmental attitudes are of slight effect. Synkineses show an augmenting influence. Respiratory arrest diminishes the movement to a sensible degree. (4) Choreic hyperkinesis. This consists of rapid movements of varying force and amplitude. Segmental attitudes diminish the movement in this type, as do synkineses, but respiration is without effect.

This diversity of the physiologic pictures in the hyperkineses ties up with a corresponding anatomopathologic substrate. One can best explain the hyperkinesis of trembling by involvement of the pallidum and locus niger; myoclonic hyperkinesis by involvement of the striatum (van Bogaert adds the inferior olive and dentate nucleus); the rhythmic systematized bradyhyperkinesis by involvement of the striatum; the choreic type by diffuse involvement of various subcortical centers—notably the corpus luysii. These hyperkineses are examples of the automatism of motor mechanisms. In pathologic conditions the motor cell apparently reacts to excitations that would be insufficient for the normal cell. These excitatory stimuli are varied, but in the main are proprioceptive from muscles, joints and the like. Exteroceptive stimuli are of much less importance.

ANDERSON, Los Angeles.

A Study of the Capillary Circulation in the Affective Psychoses. N. A. Sheveleff, J. nevropat. i psikhiat. **8**:53, 1931.

The capillary circulation was studied in twenty-one cases of depression, thirteen of manic excitement, eleven of hypomania and three mixed cases, altogether forty-eight patients. The capillary bed of the finger at the junction of the nail was studied with the aid of the Zeiss binocular capillariscope. The patients were examined in the morning and again in the evening. In the depressions, the following observations were made: The extremities were cold, moist and cyanotic; the capillaries were seen easily; the loops were thickened and widened; there was a definite retardation in the rate of flow, and there were frequent aneurysms; there was some diapedesis through the capillary wall; giant capillary loops were seen. In the thirteen manic patients there was no stasis of the blood. The extremities had a normal color; aneurysms were not seen. Capillary loops were not elongated. The patients were also studied by the injection of methylene blue into the field of vision. In normal patients the methylene blue disappeared within two hours; in patients with depression it took six hours for the dye to disappear, but in the manic patients the dye disappeared in from one to one and a half hours.

The intradermal injection of pilocarpine and epinephrine gave the following results: When the capillaries were already dilated, injection of pilocarpine gave no results, but the injections of epinephrine resulted in a marked vasoconstriction with improvement in the circulation. The same results were obtained with the administration of atropine. In cases in which the capillaries of the nail bed were constricted, injection of epinephrine gave no results, but injection of pilocarpine resulted in a marked dilatation of the capillaries, with the formation of aneurysms; this lasted only for from twenty minutes to one hour.

The author believes that the capillary picture is different in the various types of affective psychoses. He correlates this with the sugar content of the blood, calcium, epinephrine and potassium, metabolism of which is regulated by the glands of internal secretion. The author believes that the vegetative nervous system is definitely involved in the affective psychoses, and that there is a special vasoneuronic diathesis or a dysergia of the central nervous system.

Kasanin, Howard, R. I.

The Intervertebral Discs: Observations on Their Normal and Morbid Anatomy in Relation to Certain Spinal Deformities. Ormond A. Beadle, Medical Research Council, Special Report Series, no. 161, London, His Majesty's Stationery Office, 1931.

The author has observed and summarized the results of the extensive researches on the spine by Schmorl at the Friederichstädler Krankenhaus in Dresden, where Schmorl removed and studied about 7,000 spines post mortem. Much attention is given to the development of the spine and, particularly, the intervertebral cartilage. The nucleus pulposus stands out especially distinctly in young persons, in whom it proves itself to be an organ in its own right. It is that part of the disk which plays the most outstanding rôle in pathologic changes. The author refers to the demonstration of fractures of the epiphyseal ring found in the macerated vertebrae which could not be demonstrated in the fresh specimen. It is rather startling to read, "By far, the most usual manner of origin of cartilage breaks is the action, not of coarse and violent trauma but of the imperceptible, ever active injurious influence of functional life working upon cartilages which are in some way inferior in their resistive power."

The senile changes in the cartilage are far more in evidence in any series of spines than the corresponding phenomena of adolescence, and are always more devastating in their effects. As a suggestive cause of the bulging of the cartilage into the bodies of the vertebrae, one finds a greater or lesser degree of osteoporosis of the spongiosa as a common senile change. The rupture and projection of the nucleus may also extend posteriorly, pressing on the posterior ligament. In a series of 368 spines examined, 56 (15.2 per cent) showed these formations

posteriorly. They occur usually after fifty years, and affect the lower part of the dorsal and upper part of the lumbar region. Dandy described two cases of cartilaginous tumors in the lower part of the spinal canal which he removed; these tumors had produced severe nervous symptoms. This monograph should be read in its complete form by all who are especially interested in the development or diseases and injuries of the spine.

PFAHLER, Philadelphia.

A STUDY OF CEREBRAL FUNCTION IN LEARNING: THE FRONTAL LOBES. C. F. JACOBSEN, J. Comp. Neurol. **52**:271 (April) 1931.

Macacus monkeys were trained in a series of problems requiring the establishment of definite motor habits. These consisted of opening locks and boxes to obtain food. In visual discrimination different patterns cut from thin slices of apples were used, the one to be rejected covered with quinine sulphate on the under side. The pieces were placed with precaution to avoid olfactory clues. After isolation of various amounts of cerebral tissues by thermo-electric cautery, the animals were tested on their retention of old habits and on their capacity to acquire new habits. The animals' behavior subsequent to the operation was watched for visual reactions, both pupillary and hemianopic, reactions to sound, to touch, motor disturbance, spontaneous activity and emotional changes. The lesions were verified after the completion of postoperative training by microscopic sections. Five animals had bilateral injuries to the frontal area, and one of them also had bilateral parietal lesions. Another animal had bilateral lesions in the parietal regions alone.

Frontal lesions did not affect sensory disturbances. The results indicate that: 1. Injury to the frontal and prefrontal areas has no deleterious effects on the retention of simple problem-box habits or on retention of pattern-discrimination habits. They did, however, impair the retention of complex problem-box habits. The nature of the loss was not a failure in specific reactions, but in the mode of attack employed by the animals. Likewise, destruction of parietal areas produced a similar loss of complex habits, although there was good retention of simple responses. 2. Injury to frontal and prefrontal areas did not impair the ability to learn new problem boxes and pattern-discrimination problems. 3. No permanent emotional changes were found. The author questions the localization of a premotor area anterior to the precentral sulcus, which functions in the acquisition and retention of skilled acts.

ADDISON, Philadelphia.

FURTHER INVESTIGATIONS ON THE CORTICAL ARCHITECTURE IN THE DEAF AND DUMB. E. ESCARDÓ and L. HORN, Ztschr. f. d. ges. Neurol. u. Psychiat. **135**:555, 1931.

Horn reported the case of a child, aged 4, who became deaf and dumb following an infection and whose brain on gross examination showed a small supratemporal surface. The Heschl convolution was short and of simple structure, and there was a bilateral loss of the sulcus intermediae. Microscopically, the cortex of area TB (Economo's classification) was poor in cells, and the cells were smaller than normal. The horizontal and vertical lamination was entirely lacking. The horizontal fibers were destroyed, and there was a lack of radiary fibers. The vestibularis and cochlearis were normal on the left; on the right the cochlearis was completely atrophied. The fibers of the cochlearis in the medulla were normal on both sides and ended in the tuberculum acusticum and neutral cochlear nucleus. Nothing could be determined about the state of these nuclei. In only about one eighth of the cases in the literature have there been found changes in the auditory tract in the deaf and dumb. In the case reported by Horn there were no changes noted. The vestibularis was well supplied with fibers on both sides.

Escardo and Horn report the case of a deaf and dumb child with a deaf and dumb father and a brother who suffered from a similar affliction. The patient

died at 41 years of age. The brain showed an excavation of the planum temporale. The sulcus intermedius was lacking on both sides. In the area TB, just as in Horn's case, there was a much less clear striation of the cortex, and the cells were much smaller, changes which are looked on by Escardo and Horn as characteristic of deaf and dumb brains. In addition, the present case shows something which was not found in Horn's first case: much less pronounced granular layers in the cortical area TC. The lack of findings in Heschl's convolutions in the case of Horn was attributed to the early age of the patient at death.

ALPERS, Philadelphia.

THE USE OF INSULIN FOR THE RELIEF OF SYMPTOMS FOLLOWING THE SUDDEN WITHDRAWAL OF MORPHINE. F. BRAUN, Schweiz. Arch. f. Neurol. u. Psychiat. **27**:226, 1931.

The beneficial results of treatment for morphinism with insulin, as originally reported by Sakel (*Deutsche med. Wchnschr.* **2**:1777, 1930), find confirmation in six cases of rather severe addiction included in the present contribution. Braun's experience differs from Sakel's only so far as he found that sedatives in the form of scopolamine and barbital preparations were desirable adjuvants to the new form of treatment, and that the early withdrawal symptoms were not relieved to the degree reported by the latter. The symptoms were never so severe as to necessitate a cessation of treatment, however, and were of very short duration, becoming markedly ameliorated within three or four days. Some of Braun's patients who had previously been subjected to sudden withdrawal testified to the relative mildness of the symptoms in contrast to their former experiences. In each of the six cases, morphine was completely withdrawn and insulin was administered whenever the patient became restless, since it invariably exerted a marked sedative effect. The treatment was usually continued for seven days, the daily dose of insulin ranging from 20 to 100 units. Solutions of sugar were not given until after the disappearance of the acute withdrawal symptoms. Following the disappearance of these symptoms the appetite quickly returned, the general appearance showed a marked change for the better and the patient became cheerful, usually evincing a desire to get to work. In every case the patient was highly gratified with the results of treatment, since the craving for morphine had been removed with a minimum of discomfort. As the author expresses it, a complete change of heart *(Umstimmung)* had occurred. Blood sugar determinations and other metabolic studies were not carried out. In discussing his results, Braun expresses the belief that although insulin might serve to replace the stimulating action of morphine on the parasympathetic nervous system, the metabolic changes effected by its use were the more essential.

DANIELS, Rochester, Minn.

TREATMENT OF SCHIZOPHRENIA WITH MALARIA. P. A. MINNOVICH and A. I. DORSHT, J. nevropat. i psikhiat. **7**:43, 1931.

Present psychiatric literature contains numerous favorable reports on the treatment of schizophrenia with malaria. The first problem the author had to solve was whether the blood of persons with dementia paralytica treated with malaria could be used for inoculation into schizophrenic patients. As a fact, previous experimental work showed that spirochetes disappear from the blood after it has been chilled in the icebox for twenty hours. For this purpose the author inoculated schizophrenic patients whose blood gave a negative Wassermann reaction with blood that had been chilled for twenty-four hours. One hundred and three patients were treated, fifty-seven men and forty-six women. In only 7.7 per cent were the inoculations unsuccessful. During the paroxysms, malaria was responsible for a positive reaction of the blood in 19.4 per cent of the cases; the Kahn test was positive in only 2.8 per cent of the cases. After the termination of the treat-

ment with malaria, all specimens of blood became negative. Most of the patients were young men and women in the twenties and thirties, with a disease that had lasted for from two to eight years. During the paroxysm of malaria a remarkable transformation took place. The patients acted like other sick people. They became interested, keen, sociable and less impulsive and spoke freely about their problems. The improvement lasted during the treatment with malaria but soon tapered down to its previous level within from two to three months. In a small number of acute cases the results were much better, with an improvement in 50 per cent of cases. The author thinks that malaria would be of benefit only in recent cases.

KASANIN, Howard, R. I.

NEUROPSYCHIATRIC COUNTERFEITS OF ORGANIC VISCERAL DISEASE. T. H. WEISENBURG, J. C. YASKIN and HENRY PLEASANTS, JR., J. A. M. A. **97**: 1751 (Dec. 12) 1931.

According to these authors, a variety of neuropsychiatric manifestations often mask visceral disease of etiologic significance. Visceral disease may give rise to neurologic manifestations by reason of the fact that the viscera are innervated by the vegetative nervous system. They are not only influenced by the segmental and suprasegmental portions of the central nervous system and of the emotions, but in turn are capable, when disturbed, of giving rise to a disturbance in the emotions and, by reason of reflected pain, to all sorts of peripheral phenomena. Psychic and emotional states influence the vegetative nervous system and visceral functions and vice versa. Illustrative cases are given wherein neuropsychiatric symptoms have masked cardiac, pulmonary, gastro-intestinal, pelvic and genito-urinary diseases. The causes of errors in diagnoses are traceable to faulty and incomplete examinations, to the failure of judgment and proper evaluation of neuropsychiatric manifestations, and to the fact that in predisposed persons the earliest manifestations of visceral disease may be purely psychiatric. The authors believe that, from the neuropsychiatric standpoint, disease cannot be regarded as purely psychic or purely somatic. Every disease has a somatic as well as a psychic component and should be viewed from that standpoint for both diagnostic and therapeutic purposes. Moreover, every case should be studied in the light of a total situation.

EDITOR'S ABSTRACT.

A CLINICOPATHOLOGIC CONTRIBUTION TO THE SO-CALLED ÉTAT VERMOULU. A. ESSER, Arch. f. Psychiat. **93**:639, 1931.

The author reports the case of a woman, aged 64, who died fourteen months after an accident in which she suffered a concussion. During the fourteen months she showed psychic changes and had mild attacks of dizziness, which finally led to the development of a confusion characterized by motor restlessness and convulsions. Death occurred suddenly during one of the states of excitement. The diagnosis made was cerebral arteriosclerosis. Autopsy showed emboli in the lungs, no marked arteriosclerosis and no signs of skull fracture, but in the brain there was a typical état vermoulu, showing scarlike defects of the cortex and atrophic ganglion cells, but no marked vascular changes. In addition, different parts of the cortex showed small foci and areas of cellular disappearance. In the frontal and temporal lobes there was a diffuse atrophy of the cellular tissues, with a tendency to liquefaction. In the cornu ammonis and in the cortex of the insula there was a marked hyperemia. Esser is of the opinion that this condition, which is typical of the état vermoulu, was due to the trauma and was not caused by arteriosclerosis. He advances the point of view that this may be frequently the cause of such states, and that functional or organic vascular disturbances do not play any particular rôle in the production of the lesions. The other diffuse changes in the cellular tissues were most probably of senile type, whereas the hyperemia may have been connected with the attacks of excitement.

MALAMUD, Iowa City.

THE TREATMENT OF NEUROSYPHILIS. CHARLES R. RAYBURN and THOMAS M. BOYD, Am. J. Syph. **15**:168 (April) 1931.

By a systematic and individualized plan of treatment, Rayburn and Boyd have effected improvement in 76 per cent of their patients with neurosyphilis. They believe that general procedures, such as regular habits, freedom from worry and quiet surroundings, are important on the theory that just as an inflamed intestine or irritated muscle needs rest, so inflamed brain cells should be as undisturbed as possible. They favor mercury as a therapeutic agent, but if the patient has already had considerable mercurial treatment they use bismuth, usually in the form of potassium bismuth tartrate. The authors are skeptical of the value of the arsphenamine drugs, and contend that disaster may result when these preparations are used at the beginning of treatment. This disapproval is not extended to tryparsamide, which, they believe, is uniformly beneficial to patients with neurosyphilis. For fever therapy they prefer vaccine to malaria, because of its availability, safety and readiness of control. Spinal drainage is urged as a simple method of decreasing intracranial pressure, withdrawing toxic materials and favoring the invasion of the central nervous system by therapeutic agents. For intrathecal procedures, they recommend the cisternal route. A conservative plan for the treatment of feeble patients is outlined, including two spinal drainages a month, 2 Gm. of tryparsamide weekly, mercury or bismuth every three days, and rest and freedom from worry.

DAVIDSON, Newark, N. J.

A STUDY OF THE GROWTH OF A PORTION OF THE SPINAL CORD FOLLOWING ITS EARLY ISOLATION FROM THE CENTRAL NERVOUS SYSTEM IN THE CHICK EMBRYO. R. G. WILLIAMS, J. Comp. Neurol. **52**:255 (April) 1931.

The purpose of this study was to isolate from the rest of the central nervous system of chicks the lumbar enlargement at a time before reciprocal influences of one part on another had taken place. Operations were performed after about fifty-six hours of incubation. Small pieces of egg shell were packed in the gap left by the removal of the nineteenth to twenty-third segments, inclusive. The tail was cut off below the twenty-ninth segment. The egg shell was eventually absorbed and replaced by connective tissue, but not before it had produced a complete block. Three specimens hatched. Although rigid paralysis of the legs in extension occurred within twelve hours after hatching, the legs responded to stimulation, indicating that the isolated segment of the cord was active.

Histologic examination of the isolated segment disclosed no fibers reaching there from higher regions. The total number of cells in the isolated segment was reduced 41.4 per cent, while the cross-area of the gray substance was reduced 13.1 per cent and the white substance 43.9 per cent. The sympathetic chain on each side was intact. The animal gave apparent pain response to sharp stimulation, which leads the author to suggest that in chicks some peripheral pain stimuli may reach higher centers by way of the sympathetic system.

ADDISON, Philadelphia.

BRADYCARDIA WITH PROLONGED LIPOTHYMIA, FOLLOWING A TRAUMATIC INTRAOCULAR HEMORRHAGE. D. MANOLESCO, Rev. d'oto-neuro-opht. **9**:439 (June) 1931.

The oculocardiac reflex has been seen following orbital hematoma, with or without the presence of the globe, intra-orbital compression from suturing the sclera after evisceration and in acute glaucoma. In 1929, Manolesco reported a case of bradycardia in a patient with retrobulbar hematoma. In the present case, similar manifestations occurred in a case of intra-ocular hemorrhage. Following a blow on the left eye, the patient became blind and had slight ocular pain and headache. Vision returned partially the next morning, but toward evening it disappeared again, and there were violent ocular pains and weakness. The anterior chamber of the left eye was filled with blood; ocular tonus was 45 mm., and visual acuity was reduced to light perception. Several times during the succeeding

ten days, fresh bleedings occurred, each attended by sweating, syncope, pallor and slow pulse (50 beats per minute). Arterial tension was 12 maximum and 7 minimum. These phenomena constitute a clinical oculocardiac reflex. In order to produce such a state, a combination of sudden compression and a special vagotonic terrain is necessary. In glaucoma with sudden onset and extreme intraocular hypertension, bradycardia and vomiting are seen and may be relieved by decompression.

DENNIS, Colorado Springs, Colo.

CEREBRAL ARTERIOVENOUS ANEURYSMS. FREDERICK P. MOERSCH and J. W. KERNOHAN, J. Nerv. & Ment. Dis. **74**:137 (Aug.) 1931.

Cerebral arteriovenous aneurysm is a comparatively rare anomaly, usually of congenital origin and characterized, as Dandy has shown, by a fairly constant chain of clinical symptoms which usually extend over a long period and show a marked tendency to fluctuation. It is most frequently encountered in young adults. A bruit is a fairly constant, but not a diagnostic, sign. A roentgenogram of the head usually will disclose calcium deposits in the wall of the aneurysm. A study of the blood from the jugular and median veins, as Horton and Ziegler have suggested, may help to establish the presence of an arteriovenous fistula. The case studied by the authors is of interest because of the single communication between the right middle cerebral artery and the petrosquamous sinus, which usually is overlooked in routine pathologic examinations. The aneurysmal wall showed the histologic structure characteristic of an aneurysm elsewhere in the body, namely, much fibrous tissue, blood pigment, organized blood clot and absence of muscular and elastic tissue. The aneurysm had ruptured into the lateral ventricle and burrowed laterally into the substance of the brain. The possibility that this lesion was congenital must be considered, and support is given to this by the presence of miliary aneurysm at the juncture of the left anterior cerebral and anterior communicating veins.

HART, Greenwich, Conn.

PSYCHIATRIC EXAMINATION OF SOLDIERS IN THE RED ARMY. I. B. GALLANT, J. nevropat. i psikhiat. **1**:18, 1931.

Soldiers of the western military district were sent for psychiatric examination to the Psychopathic Hospital in Smolensk. Three hundred and thirty-five soldiers were examined. Of these, 40 per cent were found to be mentally deficient; yet they were in the army for from nine to twelve months. The next group in frequency were the men with so-called psychopathic personalities, who are an extremely undesirable, demoralizing element in the army. Owing to their explosiveness, aggressiveness and emotional instability, they set a bad example. They also supplied a large proportion of the criminal element in the army. The third group in frequency were the schizophrenic subjects who constituted about 10 per cent of the mentally deficient soldiers. The psychoses in these cases do not present any unusual features. As soon as a diagnosis of mental disease is made, the soldiers are given a discharge. Men with difficult cases of psychoneurosis are also relieved from army service. The author stresses the fact that malingering is very uncommon in the army; one must always analyze the symptoms before accepting it as an independent condition. Most of the cases of malingering occur in mentally deficient soldiers; the condition represents a very primitive type of response to difficult situations. No soldier should be accused of malingering until the case has been thoroughly studied.

KASANIN, Howard, R. I.

THE FATE OF CEREBROSPINAL SYPHILIS CASES TREATED WITH MALARIA. FRANZ GUGENHEIM, Ztschr. f. d. ges. Neurol. u. Psychiat. **131**:525 (Jan.) 1931.

There have been very few studies of malaria-treated cerebrospinal syphilis, in contrast to the many studies of this treatment in dementia paralytica. Gugenheim reports 13 or 14 cases, or 93 per cent, of cerebrospinal syphilis in which the spinal

fluid was cleared up by a combination of malaria and arsphenamine. This clearing of the fluid is not dependent on the severity of the spinal fluid changes. The Wassermann reaction of the blood was rendered negative in 12 of 18 cases, or in 66.7 per cent. There is a close relationship between the clearing up of the fluid and the success of treatment.

Of the 14 cases reported, 60 per cent of the patients were rendered free from complaints and able to work, 12 per cent were markedly improved, 16 per cent were improved, 8 per cent were unimproved and 4 per cent were rendered worse.

Behring's studies of the effect of malaria on cerebrospinal syphilis show: (1) that there is little danger to life; (2) that all cases with positive spinal fluid tests show improvement under the treatment; (3) that clearing up of the spinal fluid goes hand in hand with clinical improvements; (4) that the more recent the infection of the nervous system, the better the results.

ALPERS, Philadelphia.

NOTES ON THE BUSCAINO REACTION. V. S. PLUSHINA, J. nevropat. i psikhiat. **1**:50, 1931.

In 1921, Buscaino published a test consisting of the addition of silver nitrate to urine. In pathologic cases a black precipitate is formed, due to excretion of histamine in the urine. In dysfunction of the glands of internal secretion the amount of histamine in the organism is increased, affecting the white matter of the brain and the nuclei of the central nervous system. Such a disturbance of metabolism takes place in infections, schizophrenia, involutional melancholia, encephalitis and epilepsy. In view of the fact that the value of the reaction was questioned in epilepsy, the author decided to repeat the experiments herself. Eight hundred and ninety-six tests were performed on 55 healthy people and 32 epileptic persons. The author found that a positive Buscaino reaction was as frequently present in healthy, normal people as in epileptic persons. Further experiments with the test showed that whenever the urate content was increased, the reaction was positive. The author believes that the Buscaino reaction cannot be of value in epilepsy because it is positive in all conditions in which protein metabolism is involved. Anything that increases the amount of urates in the urine, such as exercise for example, causes a positive Buscaino reaction.

KASANIN, Boston.

MEDULLATED NERVE FIBERS ASSOCIATED WITH CHOROIDITIS. MILTON L. BERLINER, Arch. Ophth. **6**:404 (Sept.) 1931.

In this paper, which is well illustrated by drawings of the fundus as well as by microscopic sections, the author presents a case of extensively medullated nerve fibers associated with a low-grade choroiditis and with a small retinal detachment. From his microscopic studies, the author draws five conclusions: (1) that three types of glia cells can be demonstrated in the optic nerve: astroglia, microglia and oligodendroglia; (2) that only two types, microglia and astroglia, have been found in the nerve fiber layer of the retina; (3) that it appears that the rows of oligodendroglia investing the nerve fibers in the optic nerve cease abruptly at the proximal margin of the lamina cribrosa; (4) that, according to the investigations of Hortega, the secretion from the oligodendroglia seems to form the medullary sheaths, and (5) that in the retina the abnormal presence of oligodendroglia in the layer of nerve fibers may be responsible for the medullated nerve fibers.

SPAETH, Philadelphia.

THE PATHOLOGIC PROCESS IN THE POSTERIOR COLUMNS IN THE TABETIC FORM OF DEMENTIA PARALYTICA. ERIC JÄRPE, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **33**:227, 1931.

From a study of three cases of the tabetic form of dementia paralytica, the author concludes that in this disease there are two forms of degeneration of the

posterior columns: (1) a genuine pluriradicular tabes and (2) a more diffuse degeneration of the posterior columns which can be traced to involvement of the individual roots of the posterior nerves. In the second form, Järpe believes, meningofibrosis may possibly play an important rôle. KESCHNER, New York.

REMARKS ON SOME CLINICAL PICTURES ATTRIBUTABLE TO LEAD POISONING. EDWIN BRAMWELL, Brit. M. J. **2**:87 (July 18) 1931.

The author reviews his experience in lead poisoning over a period of thirty years. Abstracts are given of some of his more interesting cases. Although plumbism is not common, in its atypical form it may frequently be difficult to diagnose. The author emphasizes the importance of bearing it in mind in all obscure cases showing peripheral neurologic symptoms, and especially when there is an associated gastro-intestinal symptomatology.

FERGUSON, Niagara Falls, N. Y.

SHOULD ADENOMAS OF THE HYPOPHYSIS AND CYSTS OF RATHKE'S POUCH BE CONSIDERED AS SUPRASELLAR OR INTRASELLAR TUMORS? J. BOURGUET, Ann. d'ocul. **168**:379 (May) 1931.

Bourguet has collected from his operations embryologic and anatomic evidences to show that hypophyseal adenomas and cysts of Rathke's pouch should be classified as intrasellar and not as suprasellar. He disagrees with Cushing, who practices section of the chiasm in attacking cysts of Rathke's pouch. He believes that the intranasal route avoids producing a definite bitemporal hemianopia, the condition for which the operation is undertaken.

GRAPHIC REPRESENTATION OF MOTOR ANOMALIES BY THE METHOD OF HESS. M. MASSELIN, Ann. d'ocul. **168**:352 (May) 1931.

The method of rapidly recording the findings in disturbances of the ocular muscles, as originally suggested by W. R. Hess, of Zurich, has been carefully studied by Masselin. This method, in which red and green glasses are used to cover the eyes, and red and green are used in the pointer and on the tangent screen and recording chart, permits accurate plotting of diplopia fields if the head is maintained in accurate position.

SOME CONSIDERATIONS OF THE PRESSURE IN THE CENTRAL VEIN OF THE RETINA. P. BAILLIART, Ann. d'ocul. **168**:513 (July) 1931.

The method of determining the pressure in the central vein of the retina is described by Bailliart. He uses his dynamometer and the method he described in 1918 (La circulation veineuse rétinienne, *Ann. d'ocul.*, Oct.-Nov., 1918, and La circulation rétinienne, Paris, Gaston Doin, 1923). After a great deal of experience with this method he concludes that it is much less important than the study of the arterial pressure.

TRANSITORY DIPLOPIA IN OLD PEOPLE. M. L. GENET, Ann. d'ocul. **168**:400 (May) 1931.

Genet has noted transitory diplopia in old people. He believes that the prognosis is usually good in these cases, and that the condition is analogous to that which one sees in syphilis as a premonitory sign of tabes. In these elderly patients the cause is arteriosclerosis, which acts on the centers for ocular movements in a manner analogous to the action of syphilitic infection in young people.

BERENS, New York.

Society Transactions

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Joint Meeting, May 3, 1932

JOSEPH H. GLOBUS, M.D., *Chairman, Presiding*

PNEUMORACHIOCLYSIS AND CERVICOLUMBAR IRRIGATION IN THE TREATMENT OF MENINGOCOCCIC MENINGITIS. DR. LEON H. CORNWALL.

The injection of air into the lumbar sac, followed by drainage of the spinal fluid from the cisterna magna and lumbar region and through and through irrigation with sterile saline solution was recommended as a valuable therapeutic procedure in certain cases of meningeal inflammation. A patient with meningococcic meningitis came under treatment four days after the onset of symptoms. The meningitis was complicated by meningococcic inflammation of the right eye, manifested first by conjunctivitis and episcleritis, later gradually involving the whole uveal tract, retina and vitreous, and constituting an enophthalmitis. During the first few days the treatment consisted of the administration of antimeningococcic serum intrathecally and intravenously. Because of several negative blood cultures the intravenous method was abandoned.

For twelve days there was improvement of the meningeal symptoms. After they had remained stationary for another five days, there was a recrudescence of all clinical symptoms; the temperature rose to 104.2 F., with deepening stupor. On the nineteenth day, under gas and oxygen anesthesia, cisternal and lumbar punctures were made; the head of the bed was elevated, and 50 cc. of fluid was removed from the cisterna magna. Ten cubic centimeters of air was then injected through the lumbar needle, and the spinal subarachnoid space was irrigated with 300 cc. of sterile saline solution from the cervical to the lumbar regions, and vice versa. With the spinal axis horizontal and the occiput up, the air was allowed to escape from the cistern needle, following which there was an additional drainage of purulent material from the cerebral fluid spaces. The procedure was terminated by the injection of antimeningococcic serum into the cisterna magna and lumbar subarachnoid space.

This was the turning point, and recovery gradually ensued. On the thirty-fifth day the right eye was removed because of enophthalmitis, and meningococci were recovered from the vitreous. The patient left the hospital on the seventieth day. A spinal brace was worn for three months because of the atrophy in the spinal musculature. No sequelae have appeared during the intervening three years. It was emphasized that presumptive evidence of meningococcic infection outside the central nervous system, in the absence of proof of meningococcemia by a positive blood culture, is an indication for intravenous serum therapy.

TACTUAL IMAGINATION AND TACTUAL AFTER-EFFECTS. DR. WALTER BROMBERG and DR. PAUL SCHILDER.

The subjective aspect of neural function has been relatively neglected in experimental neurophysiology. This approach provides much information about neurophysiology per se, aside from the psychologic data obtained. Representations and images are both psychologic and physiologic: psychologic and physiologic activity are in some way two facets of one function. The newer development

in the study of representations and images and eidetic phenomena (Jaensch) shows that there is no clearcut borderline between those phenomena. Both have qualities much in common with actual perception. In the experimental studies of optic images and optic eidetic images, similarity has been seen in their perception and in the perception of the patients with pathologic conditions of the central nervous system. Although much work has been done in the field of optic imagination, thus far little has been done in the tactile sphere. We have studied tactile imagination in eight normal subjects and compared the results obtained with tactile after-effects.

The subjects were asked to imagine, with closed eyes, a touch, two or more touches and geometric figures on the skin. They were to report all their sensations, especially tactile feeling. About 300 experiments were performed. None of the subjects had previous knowledge in this field.

It was found that: 1. Tactual images have an objective and a subjective part. The subjective aspect is partly a memory image and partly a sensation on the skin; i. e., one imagines qualities of the object and one imagines changes in the skin. 2. There are tactual images without subjective components, whereas our only interest is in the tactual object. 3. Persons with strong objective images have very unsatisfactory subjective images and sensations. In our experiments we deal chiefly with the subjective part of imagination. 4. In every subject the tactual sensations and images follow the optic pictures, in spite of the fact that tactual imagination soon progresses along its own line of development and becomes widely independent of the optic imagination. The optic imagination can also elaborate independently of the tactual imagination. 5. The optic picture of the touched area of the skin is often vague and indistinct, having a rather symbolic character. 6. Imagined sensations are sometimes on the skin and sometimes under it. They are frequently mixed with sensations of temperature—warmth or cold. 7. The tactual imagination, which is in the foreground, creates in association with it a tactual background. 8. The tactual subjective imagination has an enormous tendency to irradiate to remote parts of the body. In two subjects there were sensations on symmetrical parts of the body. 9. These general rules are valid for any area of the skin on the body. 10. Tactual imagination often has a rhythmic character. 11. In every tactual imagination there is a quality of movement that is inherent in the imagination as embodied in its tingling character; in addition, there are movements of the image as a whole. 12. Several simultaneous imaginations of touches form a unit (*Gestalt*). Imagination of successive points provokes curved connecting lines between the points, sometimes through the air. More distant points are connected by slow movement along the skin. 13. In the imagination of lines and geometric figures the result is incomplete, because parts of the lines disappear. 14. A distinct tendency toward curving of lines is noted. There is marked difficulty in imagining angles and crossing points of lines; with only three exceptions, angles were not imagined in any of the experiments attempted. 15. Spontaneous multiplication of tactual images may occur, but not as frequently or intensively as in optic images.

When the subjects were asked to imagine touches and figures on the skin and then turned in the Bárány chair, the direct influence of vestibular stimulation was found. The results were surprising. It was seen that: 16. The dissociation between the optic and the tactual imagination becomes more evident when the subject is turned in the turning chair. 17. Vestibular irritation increases the tendency to movement in the image. In general, there is a consistent relationship between the direction of turning and the movements of the image. But there are many exceptions. In addition, there exists a definite nonspecific increase of movements in the images.

In tactile imagination, then, there was a marked tendency toward the construction of a *Gestalt* on the one hand and the destruction of a *Gestalt* on the other; there was a definite inherent tendency toward movement, and the tendencies toward integration and movement were increased when the vestibular apparatus was stimulated and when the subjects imagined touch.

Further experiments were performed, the technic already described being used, with the after-effects of tactile sensation. Vestibular stimulation by means of the Bárány chair was also used here. It was found that: 18. Slight touches have a distinct after-effect of rhythmic character, lasting as long as about three minutes. The duration of the after-effect varies in different persons. 19. The tactual after-effect is independent of the optic images. The tactual after-effect may provoke optic images, but even then each series goes its separate way. 20. In the after-effect the foreground of the sensational field stands out more sharply from the background than in tactual imagination. Transference of after-effect from one side of the body to the other has not been observed. 21. The effects of vestibular irritation can be well studied in tactual after-effects; they show an increased rhythmic tendency, elongations, curvings and a general nonspecific increase in the tendency to movement. With a more careful technic the specific influence of turning was: (1) movements of sensations in a direction opposite to the turning and during the turning, and (2) movements in the direction of turning after the turning had stopped; the nonspecific effect of turning consisted of a slow wandering in the direction of turning occurring some time after the turning. 22. The general tendencies of irradiation, of the formation of a background, of the effacement of certain parts of the images, of the building-up and destruction of forms (*Gestalten*), of movements and of curving of lines, and the tendency against perception of angles are identical in the after-effects, as with the tendencies in the imagination.

It is known that in cases of disease of the central nervous system tactile perception is imperfect and gives results that are identical with those described experimentally. Stengel has carefully studied these changes in patients with complications of the spinal cord. Stein and Weizsäcker found similar phenomena in studying the lability of the tactile threshold. We have observed similar changes in transverse myelitis and tabes and in a case of parietal lesion due to a bullet wound. In these investigations, then, the same tactile phenomena were exhibited under different conditions, namely, in normal persons and in various types of nervous disease with changed neural function. Although we cannot influence the basic physiologic background for touch, we can alter the psychic status. A patient was hypnotized and examined for tactile imagination after-effects. Under hypnosis, without definite suggestion, the same tendency toward disintegration of the tactile image was observed as that found in the experiments reported. Numerous experiments were performed on alcoholic patients with hallucinations; the results were again similar in type to those found in normal persons, and the rhythmic tendencies, the location of the sensation below the skin, the tendencies toward movement, the tendencies toward effacement of angles and the lengthening of lines were all present and definitely accentuated. Because of the question of vasomotor influence on these results, experiments were performed by irritating the skin of a catatonic patient who had extreme vasomotor lability. The configuration and color of the vasomotor response on the skin developed, and waxed and waned in a way that was very similar to the way the tactile sensations behaved. It is to be noted that in the experiments the touches were never made strongly enough to provoke a vasomotor response.

The general formulation is reached that in the tactile sphere pathophysiology brings to the foreground the tendencies that are present in the background of normal perception and in normal imagination. It is to be assumed that what is seen in the disintegration (*Abbau*) of the *Gestalt* is likewise present in the building up (*Aufbau*) of the perception. In the presence of a pathologic condition of the central nervous system perception allows the emergence of perceptive products that otherwise are not perceived normally.

DISCUSSION

DR. GEORGE VAN NESS DEARBORN: Despite the fact that relative movement is required for the production of every kind of afferent impulse, it is hard for

me to believe that the movements that are described in this interesting research were not actually dependent on the fundamental sense of the organism, kinesthesia. Therefore, I wish to inquire as to the subjective reports in regard to the muscle joint sense, the kinesthesia, that would be regularly suggested by these imaginary and the actual tactile-dermal stimulations. Were there not some subjective kinesthetic reports and data with regard to the movements that take place in some of these experiments?

DR. PAUL SCHILDER: In experiments of this kind an important point emerges, namely, that motion is an inherent quality in every perception as long as the perception is primitive. We studied the same problems in the optic sphere, and we did not find any primitive impressions that did not contain the element of motion. Motion is a general inherent quality in perception and in imagination. In this experiment on tactual imagination and on after-effects motion is in immediate connection with the picture. It is not an addition of kinesthetic impressions. This factor of motion comes out clearly in every sensation of tickling and itching. In the onset and in the end of every imagination and perception in the tactile and in the optic sphere as well there is motion. The impression of motion is primary. When one sees objects (optically and tactually) resting and unmoved, one arrives at this impression in a secondary and complicated way. This is one of the results of these experiments.

CONCERNING THE MORTALITY FROM ABSCESS OF THE BRAIN. DR. FRANCIS C. GRANT.

A review of fifty-one verified cases of brain abscess was undertaken to determine whether errors in diagnosis and localization or the time at which the operation was performed and the method of drainage used played the major part in lowering the incidence of recovery from this condition. Thirty-nine of the fifty-one cases were diagnosed as abscess and correctly localized. In four instances a tumor, not an abscess, was suspected, but the localization was exact. The position of the lesion was accurately forecast in forty-three of fifty-one cases, or 84.3 per cent. As will be seen in this series, errors in diagnosis and localization did not markedly increase the mortality.

Infection in the brain produces exactly the same reaction as it does elsewhere in the body. But owing to the highly specialized function of the glia cells of the brain, their defense reaction to infection is slow and inadequate. It requires more time for the brain to localize an infectious process than is necessary in other tissue.

The surgeon knows from experience that the proper time to drain an abscess coincides with its localization by encapsulation. The same rules should apply to an abscess of the brain as to similar infection in other areas. It is my firm belief, therefore, that infection of the brain in the stage of "cerebritis," before localization has occurred, is not a surgical lesion. Surgical measures in this stage do more harm than good, for the trauma involved in any attempt to evacuate the pus interferes with the defensive reaction of the brain. The results with unencapsulated infection in the brain encountered in this series bear out this contention. Nineteen such abscesses were drained, and none of the patients recovered. All of these operations were carried out within six weeks of the onset of symptoms. No abscess drained after the sixth week following its development was found to be unencapsulated.

The time at which an abscess is drained is, therefore, of great importance in determining the final outcome. Early drainage appears to be useless, meddlesome intervention. Encapsulation seems to occur from the fourth to the sixth week, unless the defensive mechanism of the brain is overwhelmed by the infection. The presence of a choked disk that reaches a definite level and does not increase is apparently a further indication of encapsulation. In this series but little could be learned from the development of the neurologic symptoms or from lumbar puncture to suggest that localization had occurred.

Of the thirty patients with brain abscesses evacuated after encapsulation was complete, twenty recovered and ten died. Twenty-seven of these thirty patients were operated on during or after the fourth week following the onset of symptoms. Precisely the same methods of drainage were used in each group; this is further evidence of the importance of delay in instituting drainage. The point of time in the development of the abscess at which drainage is employed seems to be of as much or greater importance than the method of drainage used.

In evacuating a brain abscess three principles should be adhered to: 1. The drainage should be placed at that point where the abscess most closely approaches the surface of the brain. 2. A small opening in the bone, preferably in a clean field, should be used. 3. As little trauma as possible to surrounding tissue should result from insertion of the drainage tube. A fumbling, inaccurate attempt to insert a drainage tube will almost inevitably result in spread of the infection outside the abscess wall. If the abscess can be reached and evacuated through a cannula, and if difficulty is encountered in placing a tube within the cavity, it is better to be satisfied with tapping alone without drainage rather than to traumatize the adjacent tissue by unsuccessful attempts to insert a tube. The surgeon should wait several days before again attempting to introduce the drain.

As a result of an analysis of this series of cases of abscess of the brain, it is believed that time should always be taken for careful study and exact localization of the lesion. Few abscesses require emergency operation. Delay permits of encapsulation and complete development of the defensive powers of the brain. In an encapsulated abscess, the organisms lose their virulence; fewer complications result when drainage is instituted. The simplest and least traumatizing methods of drainage are the safest. But it is my opinion that it is the time at which drainage of a brain abscess is instituted, and not the method used, that is of paramount importance.

DISCUSSION

Dr. Joseph E. J. King: Dr. Grant's paper embodies facts and conclusions that I have held for some time. How true are his statements regarding the difficulty of proof of the existence and localization of an abscess of the brain in certain cases. It is also true that in a number of cases fatal results have been due to the fact that operation was improperly timed or improperly performed.

His large series of cases, fifty-one verified abscesses of the brain, has given him sufficient data on which to base his conclusions. I heartily agree with Dr. Grant when he states that one should wait a sufficient length of time before operation is done in order to allow the broken-down, necrotic brain tissue, such as is found in "cerebritis" or septic encephalitis, to localize itself well, to become encapsulated. Further, I agree with Dr. Grant that in cases in which a capsule is not present the abscess should not be opened or drained with any type of drainage material. It is believed that a simple tapping should be done, and that further operative procedure should be deferred until encapsulation and a greater degree of chronicity have become established. Whether or not such patients would live sufficiently long for encapsulation to take place I do not know. I have had but one case in which the patient with nonencapsulation survived. He is well now, nine years after the operation.

Therapeutic lumbar punctures before operation are not advised. It is believed that ventricular puncture in the case of cerebellar abscess should be done rather than a subtemporal decompression, and before, rather than after, evacuation of the abscess, to prevent jamming into the foramen magnum. This also allows repeated ventricular taps in case of subsequent increase of pressure. I do not think that a walled-off, extradural or subdural pocket of pus should be considered or classified as a brain abscess. Abscesses of the brain following trauma, especially compound, comminuted fractures, should be grouped separately and not considered in the same category as abscesses resulting from extension of infection from the mastoid or the ethmoids or any of the other accessory sinuses.

Granting that an abscess has been diagnosed and localized, and is encapsulated, what procedure should be used? First, I wish to emphasize that no procedure

should be adopted until the original source of infection has been eliminated, for instance, the mastoid and the frontal and ethmoid sinuses. Otherwise, should one succeed in getting a temporary good result, there would still remain great danger of reinfection. In the cases of temporosphenoidal or frontal abscesses in which there is already partial drainage through the mastoid or frontal sinus wound, it is believed that the cone-shaped drain recommended by Mosher and Cahill should be used. In similar abcesses in which partial drainage has not already taken place, I should prefer the method advocated by me in 1924, provided that the peripheral portion of the abscess wall is within 2 or 3 cm. of the dura. For deep cerebral abscesses the small, soft rubber catheter advocated by Dr. Grant and used by Coleman would be the method of choice. The apparatus devised by Dr. Grant for insertion of the catheter impresses me as most ingenious. Fairly good results have been obtained following the use of all of these procedures. I have had no experience with the simple tapping advocated by Dandy. The stiff, rubber-tube drain should not be used for any cases, unless possibly in a case of traumatic abscess in which a sinus or fistulous tract has already been established.

There is still some question in my mind as to what is the best procedure in the case of a cerebellar abscess.

DR. IRA COHEN: One cannot help agreeing with most of the statements made by Dr. Grant. However, in recent years, no matter what method of drainage I have used in the treatment of abscess of the brain, I have not been satisfied that any one method employed answers in every case. Of late it has seemed to me that the two-stage operation is advisable, unless one is fortunate enough to place the incision where adhesion has occurred between the cortex and the dura. I think that if one knew exactly where to place the incision one would in the majority of abscesses find such adhesions and be able to carry out the operation in one stage. In the last three abscesses that I have operated on I have been so fortunate. Probably in the next three I shall not be.

DR. FRANCIS C. GRANT: We realize that methods of treatment other than the one suggested might well be used in these cases. My purpose in presenting this paper was to try to arouse discussion as to surgical procedure at least and to learn from other men their experiences with other methods. Our experience has been confined to the use of soft tubular drainage, and we are sufficiently well satisfied with this method of attack. As far as ability to localize the lesions is concerned, the record speaks for itself. The one thing that we are not sure of is the time at which the operation should be performed. I think that that is the crux of the situation. I think that almost any kind of drainage will be successful, provided the defenses of the brain have been permitted sufficient time to localize the abscess — to organize against the infecting organisms and to attenuate their virulence. These are the optimal conditions for operation. A cure is much more likely to result under these conditions than when hasty surgical intervention is attempted.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

TRACY J. PUTNAM, M.D., *Secretary*

Regular Meeting, May 6, 1932

The four hundred and first meeting of the society was held in conjunction with the Harvey Cushing Society at the Peter Bent Brigham Hospital on May 6, 1932. Dr. W. Jason Mixter presided. The minutes of the previous meeting were omitted. Dr. Cushing presented a clinic of cases of tumor of the brain. About one hundred and fifty members and guests were present.

PHILADELPHIA NEUROLOGICAL SOCIETY

Regular Meeting, May 27, 1932

A. M. ORNSTEEN, M.D., *President, in the Chair*

MULTIPLE SCLEROSIS IN FATHER AND DAUGHTER. DR. M. A. BURNS.

Of all the cases of multiple sclerosis that have come under my observation in the wards of the Jefferson Hospital during the past five years I have never, until the present instance, found the disease existing in more than one member of a family. Likewise, in the wards of the Philadelphia General Hospital, so far as I know, no report has ever been made of the presence of the disease in several members of a family. Cases of familial multiple sclerosis are extremely rare, but from time to time reports have appeared in the literature concerning the existence of the disease in two or more members of one family. Whether or not multiple sclerosis should be grouped with familial disease, however, has not as yet been definitely established.

Eichhorst (*Virchows Arch. f. path. Anat.* **146**:173, 1896) reported the case of a woman who had the disease prior to the birth of a son; the disease later developed in the child, who died at the age of 9. Two children, born before the mother showed symptoms of the disease, did not have it. Klausner (*Arch. f. Psychiat.* **34**:841, 1901) recorded a case in which a brother and sister suffered from multiple sclerosis. Weisenburg reviewed two cases in a brother and sister who were born in England. Reynolds (*Brain* **27**:163, 1904) wrote about two families, in one of which an English woman and her two brothers were affected. Allen (*Lancet* **2**:701 [Oct. 1] 1927) reported the disease in two sisters and a brother. The most recent contribution is by Robinson and Robinson (Eight Cases of Multiple Sclerosis in Three Generations of One Family, *J. A. M. A.* **92**:892 [March 16] 1929); these authors treated a family in which eight cases of multiple sclerosis occurred in three generations.

My first case is that of a man, aged 37, born in Ireland, a dyer who came to the hospital in December, 1931, complaining of difficulty in walking, pain and numbness in the right arm and leg, occasional attacks of frontal headaches, constipation and sphincteric disturbance. The onset was in May, 1930, with numbness and tingling in the lower extremities. After an attack of influenza in December, 1930, he noticed trouble in walking; his feet became stiff, and he had difficulty in bending his legs, especially the right one. The condition of the legs became more pronounced and more spastic, and he dragged the right leg when walking.

The father of the patient was living and well; the mother died in childbirth. Two brothers and five sisters were living and well. The patient's general health had always been good.

Examination in December, 1931, revealed hyperopic astigmatism and some pallor of the disks, a slight decrease in reflexes in the upper extremities, mild ataxia and a weaker grip on the right side. Both lower extremities were spastic. The patellar and achilles reflexes were increased. The Babinski sign was present on the right and slightly so on the left. The Oppenheim and Gordon signs were elicited on the right. The vibratory sense was decreased on both sides, and there was sphincteric disturbance. Laboratory studies, including the Wassermann and Kahn tests, examinations of the spinal fluid and of the urine and chemical examination of the blood gave negative results.

The patient was given ten diathermic treatments and was discharged in an improved condition.

He was readmitted to the hospital on Feb. 5, 1932, complaining of difficulty in walking, spasticity and ataxia. No definite changes were found. He was not so spastic as before and walked better than on the first admission. The outstanding features were nystagmus, spasticity and increased reflexes of the lower

extremities, together with a bilateral Babinski sign. Again the blood and the urine proved to be normal. The condition of the eye remained the same. The patient was discharged, improved, after a second course of ten diathermic treatments.

The second case was that of a girl, aged 14, who was admitted to the Jefferson Hospital in January, 1932, because of inability to walk, difficulty in talking and in using the hands, tremor of the hands, diplopia and sphincteric disturbance. The onset was in January, 1930, when she returned from school feeling nauseated. After vomiting she remained in bed for several days, when she suddenly became cross-eyed. The condition was diagnosed as a paralytic internal squint of the right eye. In the summer of 1930 she had diplopia for two months. She returned to school and felt well until November, 1930, when vision became dim and blurred to such a degree that she could not read. The condition was corrected by glasses. In December, 1930, while at school, she felt ill and dizzy and collapsed on the floor. For the next few weeks she was weak, nervous and tremulous. Following this illness she began to stagger when she walked and shook her head to and fro. The gait gradually became more unsteady, until by July, 1931, she could not walk without assistance. In February, 1931, she began to have great difficulty in pronouncing words. One of the first symptoms was weakness of the hands, especially the right. The hands were clumsy. The speech later grew more and more difficult to understand, and the jerky condition of the hands became progressively worse.

Except for an attack of influenza in May, 1930, the general health had always been good. The mother was alive and well; the father had multiple sclerosis. One brother and one sister were reported as living and well.

The outstanding features were nystagmus, shaking of the head, difficulty of speech, ataxic gait and lost abdominal reflexes. There was marked weakness of the right arm and hand, with decreased biceps and slightly decreased triceps reflexes and adiadokokinesis. In the lower extremities both feet were deformed, having high arches and insteps and marked extension of the toes. Weakness was present on both sides, but was more pronounced on the right. There were bilateral exaggerated patellar and achilles reflexes, bilateral ankle clonus, bilateral Babinski sign, bilateral Oppenheim and Gordon sign and right footdrop, in addition to lost vibratory sense and marked ataxia.

Chemical examination of the blood, spinal fluid and urine and roentgen examination gave normal results.

DISCUSSION

DR. JOSEPH C. YASKIN: There are two siblings in the wards of the Philadelphia Hospital with similar conditions. The sister clinically appears to have multiple sclerosis, which started rather late in life. The brother has been in the Philadelphia Hospital for some years and was shown some months ago at a meeting of this society as presenting a case of cerebellar ataxia. I examined him two years ago and thought that he probably had multiple sclerosis. I am not sure of the diagnosis in these cases. I believe that a final diagnosis will be based on the pathologic studies.

DR. ALFRED GORDON: It is interesting to note that this man had a cold when the disease started. Is the infection in this case the main cause of the organic condition? To Dr. Burns statistics I may add two cases in sisters who had multiple sclerosis, known to me through Dr. Stiles.

DR. M. A. BURNS: The most unusual and outstanding case reported was that reviewed by Eichhorst, but in a later review Mueller said he believed that the condition was one of myelo-encephalitis disseminata. Clinically, my cases have the typical symptomatology—nystagmus, intention tremors, bilateral tract lesions and lost abdominal reflexes—all of which are considered clinical signs of multiple sclerosis. If the condition followed an infection, one would undoubtedly consider it an encephalomyelitis disseminata.

As to treatment: No one as yet has determined a specific treatment for multiple sclerosis; the cause is unknown. Various treatments have been attempted. Two years ago at Jefferson Hospital we inaugurated diathermy for these patients. A number of patients have been treated by diathermy, and the improvement at times has seemed almost miraculous. It is still too early to determine the effectiveness of diathermy in the treatment of multiple sclerosis, but that it does help these patients considerably is assured.

A Case of Hemianesthesia. Dr. Frederick Kalteyer.

I present this woman, aged 25, as having a case of hysterical hemianesthesia. Three years ago her parents died rather suddenly, three months apart. The grief occasioned by these deaths caused a mental depression. She also worried over the state of her health. She became forgetful. In November, 1931, she had an attack of amnesia. On several occasions, while walking, she suddenly fell to the ground; she attributed this to a loss of power in the legs. The attacks were transient, for she would get up and then continue walking. Muscular power in the limbs was good. There was no loss of consciousness during these spells. Whether the seizures were of a vertiginous nature or conformed to the condition known as abasia cannot be definitely determined. She stated that, because of grief, depression and worry, she tried to commit suicide by inhaling illuminating gas about a year before presentation. This attempt at self-destruction was, however, arranged so that it would surely fail, for before turning on the gas she called up a friend and informed her of what she was about to do. In May, 1931, tremor of the right hand and arm developed; it has continued since. She was able to walk until she was admitted to the Jefferson Hospital last December.

Examination revealed corneal anesthesia and marked concentric contraction of the visual fields. Sensation was absent over the entire right half of the body. This conspicuous defect was unknown to the patient until her attention was directed to it during the examination in the hospital. The hemianesthesia involved all forms of sensibility: light touch, pain, heat, cold, deep sensibility and tactile discrimination. Pricking the anesthetic right leg during sleep did not arouse her, while pricking the left leg awakened her promptly. The right half of the tongue and pharynx were also insensitive. It was observed on some examinations that the anesthetic boundary over the trunk was sharply defined by the midline, while on other occasions it extended slightly to the left of the median position. This variation in the anesthetic zone was checked several times. There were loss of taste on the right side of the tongue and an impairment in the sense of smell. Hearing appeared normal.

A coarse, rather slow, rhythmic movement of the right hand and arm was present both when the limb was at rest and when it was in use. This flapping movement of the hand was intensified by slight pressure on the forearm. The examination itself had the effect of aggravating the symptom. Attempts to restrain the movements of the arm by holding the hand and forearm invariably induced jerky movements of the rest of the body. The tremor was always present during sleep and also under hypnosis. It has never disappeared. Several months ago, a spastic contraction of the left hand developed, which promptly subsided under hypnosis. The power of the extremities on both sides seemed normal. All of the tendon reflexes were active. The plantar reflex was normal. The sense of position of the right leg and arm was lost, the left leg and arm being physiologic. Reactions of degeneration were absent. There was no wasting of the extremities or trunk. The Wassermann tests of the blood and spinal fluid were negative; a blood count was normal, and examination of the urine gave negative results.

DISCUSSION

Dr. Frederick Kalteyer: The poisoning by illuminating gas that occurred in this case preceded the symptoms of the present illness. The symptoms of gas

poisoning were mild and required no treatment. The tremor of the right hand was present during sleep, an observation confirmed by interns and nurses. Pronounced contracture of the left hand developed, which promptly disappeared during hypnosis.

DR. BENJAMIN WEISS: I had an opportunity to study this patient at Jefferson Hospital with Dr. Kalteyer. I believe that most of the manifestations began following the psychic trauma. The death of the parents within three months of each other is an important factor. The patient has a typical hysterical personality and is extremely hypersensitive. She has hypernormal suggestibility and considerable emotional imbalance, with periods of marked depression. There is no sex basis that I could analyze in this patient. She gave me the history of attempted suicide in strict confidence; she turned on the gas jet and inhaled a small quantity of gas, with no after-effects. The window was open, and she was in good condition. She presents transient and fixed symptoms. The fixed phenomena are hemianesthesia and a coarse tremor which becomes progressively worse during examination or during emotional disturbance. She has many fleeting phenomena such as deafness, which also clears up quickly. One morning, during an examination, a spastic condition and marked contracture of the left upper extremity developed. This persisted during the examination, but under hypnosis the contracture cleared up. During the hypnosis the suggestion of a return of function was made, with spontaneous return of muscular power. Her mental reactions are purely infantile. She craves attention and gets a good deal at the hospital. She cannot adjust herself to the difficulties of returning home to two sisters, and there is a condition that one might term chronic invalidism. I do not think that this patient received sufficient gas to cause specific lenticular poisoning. The picture impresses me as one of purely psychogenic origin. The hypnosis seems to intensify the tremor. A few days ago I had occasion to tell this patient that she was about to be discharged from the hospital. She believed that her stay in the hospital was threatened, and did not awaken one morning—a kind of retaliation. I am dubious about the tremor continuing during sleep. I cannot believe that it occurs during sleep unless I actually see it.

DR. ROSS H. THOMPSON: Did the motor symptoms come on after exposure to gas? Recently I have seen pathologic evidence of cerebral changes from exposure to gas poisoning when there had been an apparently complete recovery within a few days. Within a brief time, symptoms of cerebral disturbance developed, followed by death.

DR. ALFRED GORDON: This case is most extraordinary. If it is psychogenic, the tremor should disappear in sleep. Since the tremor does not disappear in sleep, there must be an organic element. It reminds me of the case of an elderly woman who had a typical picture of parkinsonism after an attack of encephalitis; tremor of the right arm identical with that in this case developed. I wonder whether there is an organic condition with hysterical manifestations.

DR. FREDERICK KALTEYER: I am still puzzled as to whether the tremor of the hand is organic or hysterical. It continues during sleep, which is against the diagnosis of hysteria.

PICK'S DISEASE: A PRELIMINARY REPORT. DR. EDWARD D. HOEDEMAKER and DR. ROBERT A. MATTHEWS.

During the past year, three unusual cases have been studied in the psychopathic department of the Philadelphia General Hospital and Philadelphia Hospital for Mental Diseases; they are of interest because they have presented problems in diagnosis. In considering diagnostic possibilities, Pick's lobar atrophy was suggested, and on further investigation it was found that these cases fit well into this category, although the diagnosis of the condition is difficult to make on clinical grounds alone. Our purpose in presenting these cases at this time is to draw attention to Pick's atrophy, a disease which to the best of our knowledge

has not been described hitherto in the British or American literature, and to attempt to ascertain whether or not a clinical diagnosis can be made.

In 1898, Arnold Pick described the symptom complex and pathologic entity that bears his name. His first case was that of a white woman, aged 67, in whom during four years slowly but steadily loss of memory and speech disturbance in both the expressive and the receptive spheres developed. Rote or automatic memory was remarkably preserved. The speech regressed from the normal complicated structure to simple meaningless jargon. Spontaneous speech was almost entirely lost. The absence of paranoid trends or bizarre actions, together with the steady progress of the illness, seemed to set it apart clinically from ordinary senile or arteriosclerotic dementia. There were no apoplectiform episodes or convulsive seizures. Neurologic examination gave essentially negative results. Pathologic studies of the brain revealed convolutional atrophy of the entire cortex, which was greatly accentuated in the left temporal lobe and in the third left frontal convolution. Although the blood vessels showed no particular involvement, Pick was inclined to attribute the changes to vascular disease superimposed on the usual senile involutional process. We owe to Richter Stertz and Gans the demonstration that Pick's atrophy is not related to vascular supply but more probably corresponds to the cyto-architectonic areas of Brodmann, and therefore is probably a heredodegenerative process. Subsequent investigators have, in the main, arrived at the same conclusions. Most cases have shown a left frontal or temporal lobe atrophy, but in some the process has been more widespread and has involved the opposite side. Parietal and occipital lobe atrophy have also been observed, and at times there has been involvement of the caudate nucleus and anterior and lateral thalamic nuclei. A detailed description of the microscopic findings is not within our province, but it is on this ground chiefly that Pick's disease is distinguished from other related processes. Loss of the ganglion cells of the outer three and the fifth and sixth cortical layers is noted chiefly. The fact that these layers have much to do with association and little with projection fibers is of importance in producing the clinical picture. Senile plaques and Alzheimer's argentophilic bodies are absent.

From a study of the clinical descriptions in the literature, we conclude that it is a disease of the fifth, sixth and seventh decades of life, and that the outstanding symptoms are a gradual steady development of disturbance of speech and loss of memory. The course is steadily downhill, and convulsions and vascular insults are lacking. The differential diagnosis is difficult. Arteriosclerosis can usually be excluded by the finding of normal retinal vessels, the absence of any marked sclerosis of the peripheral vessels and lack of symptoms, such as irritability, vertigo or peripheral palsies, after a course of several years. Syphilis must be ruled out. The age of the patient and the clinical picture should preclude a diagnosis of senile dementia, but it may be impossible to dispose of the diagnosis of Alzheimer's disease. However, the slightly greater age, the less rapid progress and the less complete physical dilapidation should suggest the possibility of Pick's disease. The diagnosis may not be definitely confirmed until autopsy.

The case we report is one of the three studied and appears to be the most characteristic. The patient was a white woman, aged 54, who was born in England; she came to America at the age of 15. Her schooling was meager. She had the usual illnesses of childhood, without complications. She had been married three times and had had three children; two died in infancy of unknown cause. There was no history of the use of alcohol or drugs. She was described as being rather retiring and inclined to stay at home, but was neat in appearance and agreeable in her relations with others.

The patient has been perfectly well until four years ago. Then, while in a motor boat with her husband, it was noticed that she apparently became forgetful, and when steering allowed the boat to wander from its course on several occasions. Her attitude toward this was one of indifference. During the ensuing year, the only symptom was a slight forgetfulness concerning house-

hold duties. Once she hid $30 for safe-keeping, and when unable to find it broke down and cried, saying that she had been robbed. The money was later found carefully hidden in a drawer. At the death of her mother, six months later, the patient was not deeply affected and cried but little. Following this she became rapidly worse and wandered about the neighborhood for no particular reason. She became careless about her housework, was unable to cook meals and in ordering groceries bought many articles for which she had no use. Many times, at 2 or 3 a. m., she would sit upright in bed, staring ahead of her. On one occasion she said that she saw a man standing in the door, she did not remember the incident on the following day. She offered no complaints, and there were no delusions concerning friends, neighbors or husband. She was unable to read or write at this stage, whereas she had done these well before. Her appearance became untidy, and her memory exceedingly bad.

On admission to the hospital, the patient was quiet, sat alone all day and offered no complaints. She never spoke spontaneously, but cooperated to the best of her ability. Hallucinations or delusions were denied, and there was no evidence of them. She appeared apathetic, but when questioned said that she was happy. She was fully conscious but completely disoriented in all spheres. She replied to most questions with the words, "I don't know." Recent memory was almost completely lost. Remote memory was severely affected. She could just remember her name and that of her husband, but little more. She was able to learn the date if it was repeated to her. Insight was lacking. The patient was aphasic in both receptive and expressive fields. Examination in this respect was difficult because of the loss of memory. She understood words spoken to her and obeyed simple commands if they were carried out immediately. She could write her name and a few simple words of three or four letters. Reading ability was likewise limited. Abstract terms held no meaning for her, but she could name simple objects by sight and could give their uses. Stereognostic sense was then intact. Physical examination gave essentially negative results. There was no evidence of vascular disease in the peripheral arteries, heart or retinas. The blood pressure was normal. Neurologic examination also gave essentially negative results, except for questionable slight right facial weakness, central in type. There was a slight deviation of the tongue to the left at times. Roentgen examination of the skull showed nothing pathologic. Serologic and other examinations showed that the blood and spinal fluid were entirely normal.

During the past year, the only changes in the condition have been a gradual but progressive advancement of the symptoms. When examined one year after admission to the hospital, the loss of memory was still greater. At present she can remember only her own name and her husband's first name. She has forgotten her children. Disorientation is complete. There is no evidence of delusions or hallucinations. She is now unable to write her name or the simplest words and cannot read. She has complete astereognosis. She can carry out only a few commands, and cannot give the use of simple articles. There is no spontaneous speech. When asked to imitate gestures she will repeat the command rather than obey it. Her responses to questions are usually single words or the words, "I don't know." She is incontinent.

An encephalogram was made, 230 cc. of spinal fluid being withdrawn. Severe cortical atrophy was noted, with no disturbance of the ventricular system.

DISCUSSION

DR. HOEDEMAKER: The differential diagnosis must be made between Alzheimer's and Pick's disease. I do not know of any differential point that might be used, unless it is the rapidity of the development of symptoms. The progress has been slow, extending over four years—something not usual in Alzheimer's disease. I would, however, hesitate to use this fact in distinguishing between the two diseases clinically.

RIGHT BILATERAL HOMONYMOUS, UPPER AND LEFT LOWER QUADRANTANOPIA. DR. ROSS H. THOMPSON.

This man, a patient of Dr. William G. Spiller, is presented for two reasons: first, because of frequent and marked changeability of the symptoms; second, because of a most unusual cutting in the fields of vision. He is 31 years of age and was in good health until Nov. 1, 1931 (six months before admission), when he first noticed difficulty in controlling the movements of the left lower limb. The member became useless, although he states that it was not weak at that time. Within the next ten days difficulty in talking, some impairment in vision and clumsiness in the movements of the hands developed. After two weeks, an almost spontaneous remission of the symptoms occurred and continued for a month. Then he noticed a slight tendency to stagger, as if he were intoxicated, and also a mild degree of weakness in both lower limbs. Aside from these symptoms, he remained in fairly good health until March 1, 1932, when he experienced marked weakness and incoordination in both lower limbs and in the upper left limb. Again, after a few days there was a slighter degree of remission. Weakness in the left upper limb disappeared, but the lower limbs remained unchanged. On about May 10, 1932, three weeks before admission, the right hand and arm suddenly became almost useless, not because of weakness but because of incoordination. The difficulty in speech and in vision returned and, within a few days before admission, difficulty in swallowing was added.

He was well developed and showed only neurologic impairment. He presented bulbar speech and mental instability. At times he wept, but most of the time he was euphoric. There was a markedly positive Romberg sign. He could not stand without support with the eyes closed. The gait was staggering, sometimes to the left, but more often to the right. Without the use of a cane he could not take more than a few steps. The pupils were unequal, the right being much larger than the left. He had a horizontal nystagmus, accentuated jaw jerks and a right central facial weakness. There were: paresis of all four extremities, especially of the upper right with hypotonia of that extremity; marked dyssynergia in all movements of the right upper extremity, the trunk and the lower extremities, and accentuation of all the tendon reflexes, more on the right in the upper limbs and more on the left in the lower limbs. The abdominal and cremasteric reflexes were present. There were bilateral ankle clonus, which was more marked on the left, a positive left Babinski sign and a bilateral Chaddock sign. In short, there was involvement of both pyramidal pathways, with pseudobulbar palsy, involvement of the cerebellar pathways, involvement of the visual pathways and possibly involvement of the vestibulo-oculogryric pathways, with no disturbance in either vital or gnostic sensibility.

Laboratory studies revealed normal blood counts and a negative Wassermann reaction of the blood and spinal fluid. The colloidal gold curve read 5543323000. Fourteen lymphocytes were present in the spinal fluid, with 4 units of globulin and a pressure of 200 mm. of water. The urine was normal on three examinations. Roentgenograms of the skull by Dr. K. Kornblum revealed no evidence of anything abnormal. Examination of the fundi by Dr. A. G. Fewell on April 2, 1932, showed no atrophy or choking and no visual changes or other lesions.

As a routine measure and because of the patient's complaint of visual disturbance, the fields were taken by Dr. Wentworth, in the service of Dr. Holloway. They showed a left homonymous inferior quadrantanopia and a right homonymous superior quadrantanopia.

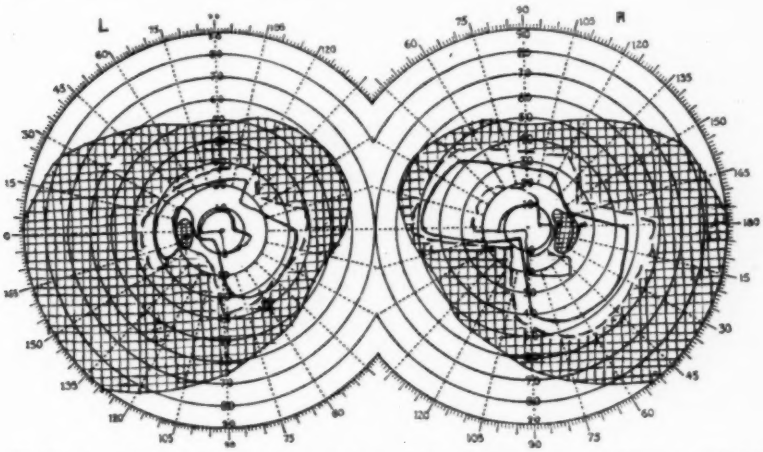
Comment.—Dr. Spiller and his staff, because of the unusual visual fields, considered the possibility of a lesion of the right temporal lobe developing first, involving the upper fibers of the optic radiation; also the possibilty of a lesion in the left temporal lobe catching the lower fibers of the left optic radiation. They likewise held under advisement the possibility of a lesion involving the occipital lobes and affecting the calcarine fissure on each side.

A bilateral upper neuron paralysis could have accounted for the pseudobulbar symptoms, the difficulty in speech, the dysphagia and the emotional instabil-

ity. The lesions were not considered vascular. The man was only 31; there was no evidence of syphilis, and there was no indication of arteriosclerosis. The possibility of a tumor in the posterior fossa or a tumor in each temporal lobe could not be ruled out at this time.

Within two days after admission, there was decided improvement in all the symptoms. An examination, twelve days after admission, revealed that the right side of the face was almost normal in activity and that articulation and speech were greatly improved. Ability to swallow liquids and the muscular power and control of the upper limbs were practically normal. There was no disturbance of equilibrium. The biceps and triceps reflexes were still exaggerated bilaterally, as were also the patellar and achilles reflexes. The lower limbs were normal in strength.

Because of this almost complete remission of the symptoms within a brief period, a second examination of the fields was made; it showed only a slight indication of what had been found at the previous examination. There was bilateral, slight concentric contraction, with only a mild degree of defect in the superior right and inferior left fields.



Field of vision of L. R. The vision of the left eye was $6/22 - 1$, reliability good; the vision of the right eye, $6/22 + 1$.

Visual field showing a left homonymous inferior quadrantanopsia and a right homonymous superior quadrantanopsia occurring in a case of acute multiple sclerosis or acute encephalomyelitis disseminata.

While there was extreme difficulty and uncertainty in the diagnosis on admission, the great and quick improvement removed that difficulty within a short time, so that it was the opinion of Dr. Spiller and members of his staff that multiple lesions, not of neoplastic nature, were probably accountable for the symptoms.

Remissions had been noted in the history before admission and in the observation and study of the symptomatology while the patient was in the hospital. The diagnosis after the second visual field report was acute encephalomyelitis disseminata, or possibly, preferably, acute multiple sclerosis.

The patient was discharged at his own request, greatly improved in all respects, apparently in a period of almost complete remission of this illness.

DISCUSSION

DR. WILLIAMS B. CADWALADER: In Dr. Thompson's case of disseminated encephalomyelitis it is difficult to explain the quadrantic defects that he has

described, one of the superior visual field of one side and one of the inferior visual field of the opposite side. Dr. Thompson has suggested that separate lesions, one in each temporal lobe, might produce such visual fields if the optic radiations were affected in that region. It is important to recall, however, the experimental work on rabbits and monkeys which was reported by Brouwer in 1927 under the title, "Projection of the Retina in the Brain." He found that in these animals there is, to a certain degree, localization of the peripheral quadrants of the retina, not only of the optic radiations, but also in the optic nerves and in the chiasm. His experimental findings correspond to the results of Henschen and Wilbrand in man. Brouwer's experiments indicated that the fibers from the upper part of the retina generally cross dorsally in the chiasm, and those from the lower half, ventrally. Brouwer called attention to the fact that tumors of the hypophysis often cause an early defect in the superior temporal quadrants of the field of vision, since the tumor often presses first on the ventral border of the chiasm and consequently damages the function of the inferior quadrants of the retina. It can be deduced that pressure on the dorsal surface of the chiasm may first cause defects in the inferior quadrants of the field of vision. The projection is approximately the same in both the crossed and uncrossed tracts.

I have called attention to these anatomic facts and wondered if they might not throw some light on the explanation of the visual fields that Dr. Thompson has described in his patient.

DR. ROSS H. THOMPSON: There was no evidence of temporal pallor of the disks.

EPILEPTIFORM CONVULSIONS PRODUCED BY STIMULATION OF THE LABYRINTH. DR. E. A. SPIEGEL.

Localized intoxication by strychnine was used to find the area where labyrinthine impulses enter the cortex. After intoxication of the dorsal parts of the gyrus suprasylvius and ectosylvius posterior, rotation of the animals (dogs and cats) produced epileptiform convulsions. These usually started in the lid and ear muscles; in some cases, a generalized status epilepticus was finally produced. Intoxication of the middle or anterior parts of the arcuate gyri or of the frontal lobe had no such influence. Extirpation of the frontal lobe, cranial from the motor area, did not prevent the production of these convulsions. Strong acoustic stimuli were also capable of producing the convulsions after the intoxication of the gyrus suprasylvius and ectosylvius posterior, but painful stimuli, strong concussion, stimulation of the centripetal fibers of the vagus or passive movements of the eye were unsuccessful in producing them. A nearly total extirpation of the cerebellum or bilateral severance of the posterior longitudinal fasciculus (Aronson) did not prevent their production. The experiments suggest that labyrinthine impulses enter the temporal lobe by extracerebellar pathways. If this region is hyperexcitable, one can produce epileptiform convulsions by labyrinthine stimuli.

DISCUSSION

DR. WILLIAM G. SPILLER: Dr. Spiegel's experimental work is important. Do the findings on the vestibular cortical center, as determined in animals, when applied to the human cerebral cortex imply that the vestibular center is in close association with the cochlear center, i. e., the center for hearing?

DR. TEMPLE FAY: The importance of these observations cannot be overemphasized, because Dr. Spiegel has clearly shown that, with strychnine, the sensory cortical areas are capable of permitting a diffusion stimulus to reach the motor areas and to produce a convulsive seizure. That the cortical sensory field, when affected by strychnine, is capable of producing convulsions in the presence of an ordinary stimulus suggests the origin of the convulsive seizure outside the motor area and throws considerable light on the present conception of epilepsy

and its therapeutic management. The drugs used to control the convulsive seizure are those that depress the sensory rather than the motor mechanism.

Dr. Spiegel found that removing portions of the brain, such as the frontal lobe, the occipital lobe, the corpus callosum and even portions of the motor area failed to prevent the appearance of a convulsion, if the sensory reception areas for labyrinthine stimuli, situated in the posterior portion of the superior temporal convolution, remained intact. If, however, this area was extirpated, no convulsions occurred. When the sensory area was isolated by a transcortical incision so as to interrupt the communications between the sensory and motor areas, no convulsive seizures ensued.

The observations of Frazier and Ingham showed that injuries in the parietal lobe, due to gunshot wounds during the World War, were more frequently associated with convulsive seizures than injuries directly involving the motor area or elsewhere.

That the type of organic pathologic condition limited to the motor area and producing actual cortical destruction is not responsible for the convulsive seizure, per se, must be considered from the standpoint of Hughling Jackson's law, that disease or destruction of the motor cells is followed by a lessening of their function and activity, and that a diseased motor cell cannot produce an increase in function. The explanation of seizures produced by lesions directly in the motor area must rest on the fact that functioning cells exist that are capable of increased function at times, and that inhibitory factors surrounding these specialized motor areas rather than the cells themselves have been disturbed.

The true type of major seizure, unmodified, does not occur in the presence of destructive lesions such as one sees in thrombosis of the middle cerebral artery, when the motor area has undergone complete degeneration. Modified responses may be possible from the subcortical motor levels, but the loss of the higher cell function is followed by paralysis rather than by increase of function, such as is seen in a true jacksonian response.

These experiments, carefully controlled, and followed by histopathologic studies, indicate that one must search in the sensory areas or their zones of communication for factors that may produce cortical irritation or prevent proper inhibitory influences from exerting themselves on the motor mechanism. As long as one perceives the symptoms of violent and continued motor movements in a convulsive seizure, the true motor area may be considered uninvolved by any direct organic pathologic condition. That the pathologic process may lie close to this area and interrupt the important sensory inhibitory control is more than likely. Scars, adhesions, tumors and gross degenerative lesions are frequently found in the precentral and postcentral areas, and convulsions as early manifestations are usually followed by progressive forms of paralysis, as the lesion extends into the true motor areas. That the influence of such a lesion may be entirely one of transcortical interruption rather than direct motor involvement must be considered.

In my experience, any method that may effectually improve cerebral circulation and thus enhance the higher inhibitory controlling mechanism, as well as methods directed toward the depression of sensory stimuli, in their cortical reception, have been found most effectual in controlling the major form of the convulsive state.

DR. ALFRED GORDON: Does Dr. Spiegel consider the labyrinth definitely as an epileptogenic zone? The rôle of the cerebellum is not clear, since convulsions are produced both with and without the cerebellum.

DR. ERNEST A. SPIEGEL: I believe that Dr. Fay is right in emphasizing the importance of the sensory side of the central nervous system in some forms of epileptic convulsions. For another group, however, direct stimulation of the motor zone by products of metabolism might be the cause of the convulsions. Dr. Spiller mentioned the relation between the cortical cochlear and vestibular centers. The area which is supposed to be the cochlear center in dogs and cats is large, and its borderlines are not so well known as those of this center in the

human brain. Further cyto-architectonic and experimental studies seem necessary before one can exactly localize the cochlear center in the brain of lower mammals and determine its relation to the vestibular centers. In regard to Bechterew's nucleus, Leidler made careful localized lesions; he claimed that this nucleus has nothing to do with nystagmus. The problem of nystagmus and of the vestibulomesencephalic systems becomes indeed more and more complicated. The statement of Lorente de No that the posterior longitudinal bundle is not necessary to permit reactions of the eye muscles from stimulation of the labyrinth is confirmed by my work. On the other hand, I was able to produce a vertical nystagmus after large injuries of the formatio reticularis. Conduction of labyrinthine impulses to the nuclei of the eye muscles in the midbrain may be by two routes: (1) the fibers of the posterior longitudinal fasciculus and (2) the vestibuloreticulomesencephalic tracts. If I might make a comparison with another centripetal system, the loss of the spinothalamic tract can be compensated for after its severance, as there seem to exist also other possibilities for conduction of pain to higher centers. In a similar way there seem to exist many possibilities of conduction of the vestibular impulse to the higher centers, and it seems that forms of sensation of high biologic value, like pain or labyrinthine impulses, have, besides a main pathway, secondary ways at their disposal to compensate the loss of the main pathway. In answer to Dr. Gordon's questions, I have rotated the animal whose cortex was strychninized and produced the convulsions by the rotation; then the cerebellum was extirpated, the animal was rotated again, and the convulsions could still be elicited.

SUBARACHNOID HEMORRHAGE. DR. REED HARROW.

This article is to be published in full elsewhere.

Book Reviews

Diagnostic des tumeurs cérébrales et épreuve de l'encéphalographie artérielle. By Prof. Egas Moniz. Price, 100 francs. Pp. 512. Paris: Masson & Cie, 1931.

This book is neither a handbook nor a monograph; it is a badly conceived and inadequate combination of the two. In the first 154 pages the author attempts to discuss the symptomatology and pathologic physiology of tumors of the brain, as well as localization; obviously, an impossible task in that space. Moreover, the author's statistics are derived from only 216 cases, so that he cannot speak with much authority to most neurologists.

In chapter VI, "serous meningitis" is discussed; the author includes under this heading certain forms of local arachnoiditis and of ependymitis. The use of the general term confuses the diagnosis, and a lack of clear understanding of the mechanics of the circulation of the cerebrospinal fluid makes quite dubious some of the explanations of the symptoms. Nevertheless, Professor Moniz has had a wide clinical experience with these cases, and his treatment of patients by means of intracarotid injections of sodium iodide appears to have brought about some remarkable cures. One child, aged 11, entered the hospital with headache, vomiting, optic atrophy and blindness. She was given an injection of 3.5 cc. of a 25 per cent solution of sodium iodide into the left carotid and 3 cc. into the right. Three days after the second injection the sight was beginning to return, and two and one-half months later the patient had approximately one-half normal vision. Some patients have maintained such improvement for as long as three years. The author is evidently correct in saying that the change cannot be due to the osmotic effect of injecting a hypertonic solution, for the improvement comes on after several days, and is gradual and relatively permanent. In patients later proved to have tumors of the brain, such improvement in vision also occurred, but was always temporary. The conclusion is that "There are certain cases of increased intracranial pressure which respond to intracarotid injections of iodide. These cures occur in a good percentage of the cases. This encourages us . . . to carry out the procedure . . . systematically on patients with intracranial hypertension."

Pages 197 to 232 are taken up with a review of the application of x-rays to the localization of tumors of the brain. Simple radiography and ventriculography are discussed in a rather elementary manner. Then, beginning with chapter XII, the main subject of the book is taken up, i. e., "L'encéphalographie artérielle." As he was dissatisfied with ventriculography, Moniz began to devise new methods to make the cranial contents visible to the x-rays. After about four years of patient work on the cadaver, on animals and on patients, he has developed a technic which gives beautiful pictures of the cerebral arteries without killing the patient. In many cases there is a good deal of pain after the injection; two cases of sudden death are frankly reported; but the most disturbing thing is that in about 25 per cent of the reported cases the injection was immediately followed by severe neurologic symptoms.

The technic is briefly as follows: The solution used for injection is a 25 per cent aqueous solution of sodium iodide. Because this is rapidly diluted by the blood, the x-ray film must be made almost instantly after the injection. Before the operation the patient is given 30 cg. of phenobarbital in order that he may lie quietly, and in order to prevent pain and the untoward neurologic symptoms. The carotid artery is exposed, and the injection is made into the common carotid, the external branch being temporarily obliterated. All this is done under local anesthesia. Because of the handling of the region of the bifurcation of the artery, the operator must be careful that stimulation of the carotid sinus does not cause

a lowering in blood pressure, which is dangerous. The injection usually consists of about from 6 to 7 cc. in adults and 2 or 3 cc. in a child.

The main criticism of this work is that the method of injecting the substance into the arteries of the brain is evidently accompanied by great risk to the patient. Although many of the reported cases have statements in them that there was no reaction after the injection, yet a careful analysis of the case reports shows that of the forty-five cases reported, in thirty-one there was no untoward reaction (or none was mentioned); fourteen patients had immediate reactions after the injections into the carotid: one died; four had hemiplegia; four had generalized convulsions; two had focal convulsions (one with unconsciousness); one had dysarthria, and one had paraphasia. None of these symptoms was permanent (except death), but twenty-nine of the forty-five injections were unnecessary as the diagnosis is perfectly plain in the case reports. Although this method may have value in certain obscure cases of tumor of the brain, especially in giving a positive picture of vascular tumors, it is nevertheless a procedure of definite risk and doubtful value. It would seem that the employment of this technic is unjustifiable in cases in which a neurologic diagnosis is possible.

The Psychology of a Primitive People: A Study of the Australian Aborigines. By S. D. Porteus. Price, $6. Pp. 438, with 48 plates and 3 maps. New York: Longmans, Green & Co., 1931.

Modern studies of psychology have shown that a great deal can be learned about mental disorder from the study of the behavior of primitive people. Unfortunately, not a few of the books on cultural anthropology that have been accepted at their face value by psychopathologists are not reliable as to their data, and are highly speculative in their deductions. The present book is a noteworthy exception. It embodies the results of an expedition to Australia in 1929, under the auspices of the Australian National Research Council, the University of Hawaii and the Rockefeller Foundation. The book is certainly a credit to its author and to these institutions. The author — well known as the originator of the Porteus maze test — believed that the mental test approach was inadequate for the study of the psychology of a primitive race. So he included in his task an investigation of the environment of the people to be studied, and of their social customs, organizations and habits of life.

The first part of the book contains an excellent description of the Australian environment and the daily life of the aboriginal inhabitants. There follows a discussion of the underlying psychology of the Australian social organizations, totemism, ceremonial observances and initiation rites. The last part of the book deals with results of the special mental examinations of adults and children, and with physical measurements.

The book abounds in interesting and instructive details which do not lend themselves to summary in a brief review. The author makes full use of the existing literature on the cultural anthropology of Australia, e. g., the work of Spencer and Gillen. He has some important criticisms to make of the views commonly held about the beliefs of Australian aborigines. The main conclusions are the following: The Australian aborigines are not really primitive, in the ordinary sense of the word. Considering their circumstances, they have made considerable progress in specialized directions. The current conception that their intelligence is extremely inferior is not correct. Their social usages can be understood as adaptations to a peculiar and extraordinarily difficult environment. The facts generally adduced as proof of the low and degraded mental status of the Central Australian aborigines are not entirely valid, on close examination. The author discusses specifically their nakedness, their houselessness, their poverty, their often-quoted belief that sexual intercourse is unrelated to conception and the strict tribal rule of a council of elders.

The special examinations carried out by Porteus included physical measurements, psychophysical tests, such as vital capacity, and the following intelligence tests: Porteus maze, Porteus form and assembling, xylophone (Squires-Knox),

form board (Goddard type), hand test (Thurstone-Squires), Koh's block design, digits memory test, footprints (Porteus), dot estimation (Porteus) and drawing test (Goodenough).

The physical measurements are perhaps the least satisfactory part of the investigation, but they play only a subordinate part in the study.

The book as a whole is both scholarly and readable. The subject matter is presented in an informative, narrative style. There are many excellent photographs, showing native customs, landscapes, types of persons and so on. There is a good index.

Although the reviewer cannot agree with all the author's interpretations, he thinks that the book deserves the highest praise, and that its perusal is to be recommended to all neuropsychiatrists. It throws an entirely new light on the manifold problems of the psychology of the Australian aborigines and those of primitive people in general. It is a classic of American psychologic science.

Verbrechen als Schicksal: Studien an kriminellen Zwillingen. By Johannes Lange. Price, 7 marks. Pp. 96. Leipzig: Georg Thieme, 1929.

The author has collected material on thirty pairs of twins, of whom it was true that one of each pair, at least, had been sentenced for a criminal offense. Of these persons, he regards thirteen as single ovum twins. In ten of the cases, both twins of the monozygotic pairs had been arrested and sentenced. Three had not become criminals. Of the seventeen dizygotic pairs of twins, in two cases both twins had been arrested and sentenced; in fifteen cases, one of each pair of twins was not convicted of crime. He draws the conclusion that, with respect to crime as well as to hereditary disease, monozygotic twins tend to act in the same way; dizygotic twins tend to act "discordantly." The hereditary anlage plays a predominant rôle as a cause of crime.

The author presents these conclusions in an early part of the book. There follows a full presentation of the individual cases. In the last section of the book, these conclusions are discussed more fully in their general aspects. He believes that one can draw the "absolutely certain conclusion" that it is predominantly the hereditary constitution that leads a person to crime in the present-day social environment.

To apply the "twin biologic" method to the problem of crime was a meritorious undertaking, but the author's conclusions are not convincing. It does not appear from the data he gives that the diagnosis of the monozygotic twins is established beyond doubt. He himself admits that in one fourth of these twins, only one of the pair has been sentenced. Most of his material is composed of repeated offenders.

The sensational title of the book is not without significance. Just as the author's teacher, Kraepelin, regarded schizophrenia as "Fate," so Lange now designates crime as "Fate." The psychologic analysis of the personalities involved makes easy reading, but it is not profound. There is a discrepancy between a natural science approach and such expressions as that used for one pair of twins, for example, that "their innermost nature is fraud." Among the relatives of these twins he found without exception psychopathic personalities, most of whom belonged to the weak-willed or persons "without will" (willenlos).

The final plea of the author is for well endowed means of research into the problem of crime. The book is fluently written and has found great approval in lay circles.

Histopathology of the Central Nervous System. By Prof. Dr. L. Bouman and Prof. Dr. S. T. Bok. Price, $15. Pp. 37, with 212 illustrations. Utrecht: Oosthoek, 1932.

A histologic atlas of the commoner diseases of the central nervous system, illustrated by photographs and explained by a brief text printed on high grade paper, is now available in English. The purpose of this book is to offer a simple

basis for the discussion and diagnosis of postmortem material. Doubtless, workers in laboratories of general pathology will welcome the atlas and find it useful. If accompanied by a series of lectures and laboratory exercises, the book might be of real value to students in medical schools. The 212 illustrations are beautiful photomicrographs, in many instances extraordinarily interesting. Each one is accompanied by a lucid explanatory legend. In this way a good many of the microscopic aspects of the diseases that have been considered are to be seen to advantage. The photographs are printed on but one side of the leaf. This leaves the reserve page blank, and since the quality of the sheet is that of fine drawing paper on which pen, pencil and brush sketches take well, the student here adds his own illustrations.

In the text, a few words are said about the more elementary phases of neuropathologic processes, and short descriptions of the normal and pathologic constituents of the central nervous system are given. Then follows a brief résumé of each of twenty-two diseases. Tumors are omitted, as well as several common and serious neurologic disorders, such as the hereditary group.

There is no really adequate elementary textbook of neuropathology in English or any other language, and while this book by Bouman and Bok certainly does not measure up to one's hopes, it is at least a work with some pragmatic value. Superficiality seems to be the outstanding characteristic, and a professional worker in the field of neuropathology will find the work of little value. No attempt is made to coordinate diseases, and no general principles or underlying theories are laid down. Many mooted questions are passed over as if their answers were well known, e. g., the anatomy of the ectomesodermal membrane and the participation of oligodendroglia in the abbau process. A strange combination of things simple and not so simple (mitosis of gitter cells!), together with undue emphasis on certain diseases and superficial treatment of others, suggests that the book was composed incidentally as a by-product of other endeavors, rather than deliberately in response to a need.

Grundzuge der Neurochirurgie. Vol. 8. Medizinische Praxis. By Prof. Dr. Med. Walter Lehmann. Price, 13.50 marks. Pp. 197. Dresden: Theodor Steinkopff, 1930.

This book is designed primarily to meet the requirements of the practitioner and busy surgeon, with a view to presenting in concise, condensed form the principles of neurosurgical treatment and such data as may be of value in directing the procedure of the physician concerned with the early diagnosis and treatment of the case. No attempt is made to elaborate on the intricate technic belonging to the specialty, but an effort has been made to include an unbiased discussion and personal opinion on the accepted developments in therapy as disclosed by the more recent researches.

An attempt is made to cover the whole field of neurosurgery in 197 pages under 6 main headings, which include: (1) the surgical treatment of the brain and its coverings; (2) the surgical treatment of the spinal cord and its coverings; (3) the surgical treatment of traumatic paralysis and tumors associated with peripheral nerves; (4) the surgical treatment of the vegetative nervous system; (5) the neurosurgical treatment of spastic paralysis; (6) the surgical treatment of pain. Each main section is subdivided into portions which deal with the various subtopics in turn.

For its brevity and conciseness the book gives an orderly, condensed outline of each problem of neurosurgery, including generally etiology, symptomatology, diagnosis and prognosis, together with a discussion as to the methods of treatment and results. After each subsection the more recent or pertinent references are appended. The pages allotted for each subsection are of necessity limited; nevertheless, a considerable amount of information has been well arranged in a small space. The value of lumbar puncture in the management of injuries to the head is perhaps not sufficiently stressed, and the treatment in selected cases of spina bifida might now be considered more optimistically. The volume is of value as a prac-

tical guide or condensed outline of the subject and literature. It is clearly written and conveniently bound, and the type is good.

Psychoanalyse und seelische Wirklichkeit. By Paul Maag. Price, 8 marks. Pp. 228. Munich: J. F. Lehmann, 1930.

Maag is a physician. He dedicates to the State Department of Education of Zurich an evaluation of Freud's psychology by one who prefers to work with what he experiences of himself and the human beings about him. He balks at a conception that denies man's subjectivity and self with the claim that man does not live as he thinks himself to live, but that man *"is lived"* by unknown and ungovernable forces (Freud, The Ego and the Id, p. 27). With all his otherwise freudian ideology and methodology, Maag militates against the unconscious that tries to pose as the essence of man. He wants to show how the very study of the neuroses proves the dominance of consciousness. Instead of the extreme naturalism of Freud, Maag insists on making conscious life responsible for the conflicts of conscience which he, nevertheless, with Freud makes finally also responsible for the neurosis. He startles the reader with the statement that neurosis occurs only within the sphere of Christian civilization. Mohammedanism, Hinduism and animism do not know "the neurosis." Its genesis can be grasped only from the angle of the patient's own psyche. It would lead too far to outline Maag's really interesting exposé of his own conflict with Freud's writings. To the great advantage of the reader, he always quotes definite passages of Freud's writings, in the form of an unusually painstaking exegesis carried through *lege artis*. In his revolt against freudism he makes an almost religiously fervent appeal to a kind of a common sense, an unusual mixture of appreciation and non-appreciation of freudian teaching.

Maag takes up: consciousness and the unconscious, showing his objections to the concept of the "unconscious;" Freud's exaggerations in the interpretation of the lapses and mistakes and symptomatic activities; his views on repression and resistance; the dream; the sexual theory, the neurosis theory, and a summary review of his discussions. A glossary of technical terms shows the author's desire to reach beyond the medical reader, evidently into educational circles.

Die Organneurose im Lichte neuerer Anschauungen. By Ernst Hoffstaedt. Price, 1 mark. Pp. 26. Leipzig: Fischers medicinische Buchhandlung, H. Kornfeld, 1928.

In this little pamphlet the author discusses the diagnosis and treatment of what he speaks of as "vegetative neuroses." He claims that for purposes of classification it is easy to separate psychoneuroses from "organ neuroses" (vegetative neuroses). Vegetative neuroses are the ones which both the neurologist and the general practitioner encounter most frequently. The morbid phenomena of the vegetative neuroses are limited to vegetative organs and their functions. The separation of the vegetative neuroses from organic disease is almost impossible. There are fleeting transitions.

The author distinguishes three large groups: (1) "vasoneurosis," comprising all sorts of vasomotor disorders, including certain forms of urticaria, migraine, "the vasomotor form of angina pectoris," certain forms of Raynaud's disease and hypertonia; (2) the "secretion neuroses," such as hyperacidity, hyperhidrosis and rhinitis; (3) the "dyskinesias," which include all sorts of spastic phenomena of the intestinal tract, of the bladder, dysmenorrheic disorders, bronchial asthma and the like.

Neurotic disorders are "the bodily expression of mental drives." Therapy has to be directed primarily toward the psychic components. Psychoanalysis is to be advised in severe cases only. He prefers a general guidance, such as the psycho-orthopedia of Schultz. In many cases pharmacotherapy, directed toward the vegetative nervous system, is indicated.

Considering its briefness, the book gives an adequate survey of the nosology of the phenomena included; like many other writings on neurotic phenomena by internists, especially in Germany, it is, however, highly theoretical.

The Physical Basis of Personality. By Charles R. Stockard. Price, $3.50. Pp. 305. New York: W. W. Norton & Company, Inc., 1931.

Much of the material in this book has already been published. In fact, it formed the basis of a series of lectures given by the author in 1930 at Stanford University. On the other hand, the breeding experiments on the structural types among dogs are published in this book for the first time. These experiments show that human freaks parallel in their growth and form diversified canine types, and that the growth of such types is associated with modifications in structure and functions of some of the internal glands.

It would be difficult to single out any particular chapter or statement in this interesting work. The chapter dealing with personality and structural types among normal persons, in which the author emphasizes the linear and lateral types of development, and his comments on the different personality in each are of great interest. It is a familiar fact that man's most striking deviation from his nearest animal relatives is in intellectual achievement. The author points out two particular causes for this: (1) the retention of head proportions comparable to those found in the fetal stages of the higher mammals, with the development of the disproportionately large brain and small face, and (2) the advantage man attains in the prolongation of childhood and sexual development. In all probability early ancestral man, probably like other mammals of his size, attained the adult condition within a few years, possibly as few as four or five.

It would seem obvious that the presentation of such a subject is by no means easy, but the author has presented the material in a clearcut, readable and logical form, so that even a person without any special training would understand the subject matter.

Stimme und Sprache in der Heilpädagogik. By Emil Fröschels. Price, 7.40 marks. Pp. 204. Halle: Carl Marhold, 1926.

This volume is intended for teachers of retarded or otherwise abnormal children. It gives a comprehensive survey of the different forms of speech disorders. The author presents first an anatomy of the larynx and mouth. He then discusses the physiology of respiration, the formation of the voice and normal articulation. A brief chapter deals with the development of normal speech in the infant.

In the pathologic section of the book, the author starts with a discussion of deaf-mutism and of the speech disorders of persons with impaired hearing. A few pages are devoted to the difficult problem of dumbness with intact hearing. There follows a survey of the field of aphasia, both its diagnosis and its treatment. The next part of the book is devoted to a full discussion of the different forms of stammering, the different theories of its pathogenesis and its treatment. The rest of the book deals with the general hygiene of the voice and language and the voice disorders that are found among retarded children.

The book fulfils well its purpose of serving as an introduction for teachers to this important field. There are a bibliography, which is, however, restricted to German authors, and a good index of subjects. In view of the fact that the treatment of early manifestations of slight speech disorders among children is generally so neglected, useful books like the present one deserve a distinct place in the literature.

Rééducation psychothérapique: Contrôle de l'équilibre mental et nerveux. By Pierre Prost. Price, 20 francs. Pp. 138. Paris: Gaston Doin, 1932.

This is a brief survey of the whole field of psychotherapy. The author develops a conception according to which nervous disorders are explained as the result of

a disturbance of "a mental and nervous equilibrium" that exists in a normal person. He classifies "neuropathic persons" into two groups: the agitated and excited, on the one hand, and the depressed and fatigued, on the other. The first group needs a type of "reeducation" that makes use of methods of relaxation; the second group needs types of therapeutic technic that bring into play attention and will. The whole discussion remains on a formal basis, and the general practitioner to whom the book is addressed, with the hope of arousing greater interest in psychotherapy, will miss concrete illustrative data and examples. A sharp distinction is made by the author between "suggestion" and "persuasion," for instance, without any indication being made that the working of these two factors can hardly be separated so categorically. The book is well written and its thesis clearly put. It is a pity that its clarity is gained at the expense of a more profound treatment of the subject.

Accidents, Neuroses and Compensation. By James H. Huddleson, M.D., with a foreword by J. Ramsay Hunt, M.D. Price, $4. Pp. 256. Baltimore: Williams & Wilkins Company, 1932.

This is a timely book. The traumatic neuroses have always been with us; because of the compensation laws which are well nigh universal in this country and all over the world every practicing physician is compelled to deal with this problem. Because of the economic depression many families are dependent for their livelihood on the money paid to a member of the family because of compensable injuries. The author divides his book into twelve chapters, and there is a summary at the end of each. His point of view is sane, for he has given credence to the literature on the subject, and obviously his experience is large, for his manner of dealing with the subject is sound. It would be well if all states of the Union had uniform compensation laws. As it is, some disabilities are more compensable than others in different states. This is particularly true of the psychoneuroses, which are perhaps more difficult for the average physician to understand than the usual type of organic conditions resulting from accidents.

Die Funktion des Gewissens in den neurotischen Krankheiten. By Max Levy-Stuhl. Price, 0.90 marks. Pp. 22. Schwerin: Friedrich Bahn, 1932.

This book is a reprint of a lecture given before an association of physicians and clergymen. The author presents the view that from the biologic point of view alone the neurotic patient cannot be understood. The psychic conflict of the neurotic person is in every instance based on a conflict of conscience. Conscience is an irreducible, unanalyzable phenomenon. In the course of psychoanalysis, the patient has to give up his inner resistances; he has to conquer his own self. The author sees a close analogy between psychotherapy and the religious appeasement of conscience. In the "theological postscript," by Carl Schweitzer, the author's point of view is criticized. It is pointed out that from the theological point of view ethics and religion cannot be separated. The "conscience troubles" of the neurotic person and of the normal person are identical; they can be resolved only by "faith in the spontaneous interference of God." This little volume is an interesting contribution to the problem of the relationship between psychotherapy and religion.

L'épilepsie chez l'infant et le caractère épileptoïde. By Gilbert Robin. Price, 18 francs. Pp. 150. Paris: Gaston Doin, 1932.

The author, who is a physician in a dispensary for "nervous, retarded and unstable children," discusses in this booklet his observations on epilepsy and epileptoid phenomena in childhood. The main part of his presentation is devoted to the epileptoid personality. In contrast to Hochart and others, he affirms that the "epileptoid character" can be diagnosed in childhood, even when no paroxysmal phenomena are present. As the chief epileptoid phenomena, the author describes

instability, "turbulence," impulsive outbursts of anger, violence, cruelty, enuresis nocturna and somnambulism. He lays great stress on an intellectual disorder, which he terms "obnubilation." This symptom he regards as midway between true epileptic absences and a great slowness of intellectual processes ("bradypsychia"). A number of brief case histories are given. The discussion is restricted to the French literature on the subject.

The Structure of Insanity: A Study in Phylopathology. By Trigant Burrow. Price, 2 shillings, 6 pence. Pp. 80. London: George Routledge & Sons, Ltd., and Kegan Paul, Trench, Trubner & Co., Ltd., 1932.

In this little book, which is one of the "General Series of Psyche Miniatures," the author summarizes briefly his ideas, derived from group analysis, which he has already expressed more fully in numerous papers and a book. He does not offer here any new concrete points, nor does this statement add to the clarity of Dr. Burrow's general theses. The following quotation may serve both as an example of the style of presentation and as a statement of the author's views: "It is time that the whole category of good-bad (normal) alternatives, which are sponsored only by the divisive social substantive 'I' and to which patient and doctor are alike the unwitting social victims, be regarded as superficial symptoms of a deeper-seated disorder existing throughout the human species and that accordingly we take up seriously the laboratory study of the physiology of man's behavior as a social animal" (p. 78).

Lang's German-English Medical Dictionary. Revised and edited by Milton K. Meyers, M.D. Fourth edition enlarged. Price, $10. Pp. 926. Philadelphia: P. Blakiston's Son & Co., 1932.

"Lang's German-English Medical Dictionary" has always been the standard. The fourth edition is of particular interest to neurologists, because it has been revised and edited by Milton K. Meyers, a well known Philadelphia neurologist. The book is invaluable to all students of the German neurologic literature.

The Mental Defective. By Richard J. Berry, M. D., and R. G. Gordon, M.D. Price, $2.50. Pp. 217. New York: McGraw-Hill Book Company, Inc., 1932.

This is an excellent presentation of the problem of mental deficiency written for the layman, social worker and general practitioner. The subject is dealt with chiefly from the sociologic point of view and emphasizes the responsibility of the public and the increasing cost of the care of such patients. While the book is written from the British standpoint, it is equally pertinent to conditions in this country.

The Craving for Superiority. By Raymond Dodge and Eugen Kahn. Price, $1.50. Pp. 69. New Haven, Conn.: Yale University Press, 1931.

This little booklet contains general comments on the psychology of the feelings of superiority and inferiority. The authors believe that the craving for a feeling of superiority and the feeling of superiority itself are important and almost universal factors in human psychology, both normal and abnormal. The book is written in a simple, nontechnical style and is intended for the general reader. It is a publication of the Institute for Human Relations.

Anatomie élémentaire des centres nerveux et du sympathique chez l'homme. By P. Gilis. Second edition. Price, 24 francs. Pp. 236. Paris: Masson & Cie, 1932.

This is the second edition of the book, the first having appeared in 1926. It gives an excellent conception of the anatomy of the sympathetic nervous system. Some of the illustrations are original.

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